Realizing the Promise of Pharmacogenomics: Opportunities and Challenges

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Draft Report of the
Secretary's Advisory Committee on
Genetics, Health, and Society

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About SACGHS

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) was first chartered in 2002 by the Secretary of Health and Human Services (HHS) as a public forum for deliberation on the broad range of policy issues raised by the development and use of genetic tests and, as warranted, to provide advice on these issues. The charter sets out the following specific functions of the Committee:

- Assessing how genetic and genomic technologies are being integrated into health care and public health;
- Studying the clinical, public health, ethical, economic, legal, and societal implications of genetic and genomic technologies and applications;
- Identifying opportunities and gaps in research, and data collection and analysis efforts;
- Examining the impact of current patent policy and licensing practices on access to genetic and genomic technologies;
- Analyzing uses of genetic information in education, employment, insurance, and law; and
- Serving as a public forum for discussion of issues raised by genetic and genomic technologies.

Structurally, SACGHS consists of up to 17 individuals from around the Nation who have expertise in disciplines relevant to genetics and genetic technologies. These disciplines include biomedical sciences, human genetics, health care delivery, evidence-based practice, public health, behavioral sciences, social sciences, health services research, health policy, health disparities, ethics, economics, law, health care financing, consumer issues, and other relevant fields. At least 2 of the members are specifically selected for their knowledge of consumer issues and concerns and the views and perspectives of the general public.

Representatives of at least 19 Federal department or agencies also sit on SACGHS in an *ex officio* (non-voting) capacity. The departments and agencies are the Department of Commerce, Department of Defense, Department of Education, Department of Energy, Administration for Children and Families (HHS), Agency for Healthcare Research and Quality (HHS), Centers for Disease Control and Prevention (HHS), Centers for Medicare & Medicaid Services (HHS), Food and Drug Administration (HHS), Health Resources and Services Administration (HHS), National Institutes of Health (HHS), Office for Civil Rights (HHS), Office for Human Research Protections (HHS), Office of Public Health and Science (HHS), Department of Justice, Department of Labor, Department of Veterans Affairs, Equal Employment Opportunity Commission, and Federal Trade Commission.

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Preface

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) was chartered in 2002 to provide advice to the Secretary of Health and Human Services (HHS) on policy issues raised by the development and use of genetic technologies and their integration into clinical and public health practice. Because the scope of its charge encompasses a broad range of issues, the Committee undertook a prioritization process during its first year to help focus on areas in which policy recommendations will have the greatest impact. The Committee ranked pharmacogenomics (PGx) as a high-priority issue warranting in-depth deliberation and analysis because of its potential to significantly affect health care and the important policy issues it raises. The Committee believes there are tremendous opportunities in this field yet several challenges that need to be addressed for the field to advance and to prepare society for its appropriate integration into clinical practice.

SACGHS began its deliberations on PGx with informational sessions during its June and October 2005 meetings. At the June 2005 meeting, the Committee learned about the fundamentals of PGx and the state of the field as well as the ethical, legal, and social implications of PGx. They also heard from the diagnostics and pharmaceutical industries, a public health provider, and a health care provider about their perspectives on PGx. In addition, they were updated on HHS efforts and future directions in PGx by representatives from the Centers for Disease Control and Prevention, Food and Drug Administration (FDA), and National Institutes of Health. Fact-finding continued at the October 2005 meeting with an exploration of the economic challenges associated with PGx product development and its integration into clinical practice. The Committee also heard more about the ethical and social issues associated with race and genetics in the study of differential drug response.

To guide its work on PGx, SACGHS assembled a Task Force comprised of several Committee members and *ex officios*. As its first task, the Task Force gathered information about Federal efforts to address PGx through a survey of Federal agencies (see Appendix A for a summary of these Federal activities). The Task Force also reviewed several reports on PGx prepared by other groups. The Task Force used these sources of information, including the presentations, to develop an outline of issues to be discussed in an in-depth report on PGx.

In early 2006, The Lewin Group (Lewin), through a contract with the Office of the Assistant Secretary for Planning and Evaluation, was commissioned to assist with the development of the PGx report. Lewin began its work by preparing a review of the PGx literature. Meanwhile, the Task Force used the presentations and literature review to draft recommendations. The literature review and draft recommendations were reviewed by SACGHS at its June 2006 meeting.

Following the June 2006 meeting, Lewin prepared a first draft of SACGHS's PGx report that incorporated information from the literature review, presentations, Federal efforts table, and summary of other PGx reports. SACGHS staff revised the draft recommendations to incorporate input received from SACGHS at the June 2006 meeting. The Task Force held a day-long meeting in September 2006 to discuss the draft report and revised recommendations. The draft report and recommendations were further revised to reflect the Task Force's discussion.

The next iteration of the draft report and recommendations was then reviewed at the November 2006 SACGHS meeting.

From December 2006 to February 2007, Lewin conducted interviews with 15 stakeholders with expertise on PGx and related fields to obtain their input on the November 2006 draft of the report and recommendations. During two conference calls in February and March 2007, the Task Force reviewed a summary of the interview comments and provided guidance to Lewin and SACGHS staff on how to revise the draft report and recommendations.

The current draft of the PGx report reflects the cumulative work of SACGHS and its PGx Task Force, Lewin, and SACGHS staff. The Committee now welcomes public input on this draft. After the public comment period closes, comments will be carefully considered and used to help develop the final report. SACGHS expects to complete its work on this issue in 2008.

Executive Summary

The emerging field of pharmacogenomics (PGx) arises from the convergence of advances in pharmacology, genetics and, more recently, human genomics. Among its applications, PGx has the potential to enable a new paradigm of personalized medicine. It can provide clinicians with tools to assess risks and benefits associated with using available medicines for particular patients and to select therapies and treatment tailored to each patient. In so doing, PGx should enable direct management of individual patient drug response for such disease areas as cancer, cardiovascular disease, asthma and HIV/AIDS.

Realizing the benefits of PGx on a large scale remains a long-term goal. Applications of PGx in practice to date have been notable, yet few. Nevertheless, current and emerging advances suggest that better targeted and more effective PGx-based treatments have the potential to yield significant gains in personal health, population health, and cost-effective resource allocation.

This report is intended to provide timely, policy-relevant information about PGx to help frame recommendations for the Secretary and other policy-makers and stakeholders. It examines potential opportunities for PGx to advance the development of diagnostic, therapeutic, and preventive strategies to improve health, as well as challenges posed by PGx research and potential barriers to benefiting from PGx in clinical practice and public health.

A. The Promise of PGx

PGx has drawn great attention for its potential to redirect personal care and public health paradigms in the US and abroad. It has begun to offer powerful tools for applying information about individual genetic variations and drug response for health care decisions, with the promise of "customizing" or "personalizing" health care.[1] Some early successes of PGx include the use of Herceptin for metastatic breast cancer, managing the use of the mainstay drug thiopurine 6-mercaptopurine to treat acute lymphoblastic leukemia in children, and managing the use of warfarin for those at risk of harmful blood clots. PGx is still an emerging field, and the instances of translating PGx into practice are few to date. Some in the field consider that the promise of PGx is largely unfulfilled,[2,3,4] with more modest expectations of benefits from PGx, at least in the near term.[5]

Once it becomes more fully realized, PGx may address certain major health needs, including reducing adverse drug reactions (ADRs). Current "trial and error" approaches to pharmaceutical therapy contributes to nearly three million incorrect or ineffective drug prescriptions annually.[6] In contrast to that approach, PGx has great potential to increase the safety and effectiveness of drug treatment by identifying those at risk for ADRs and by helping

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1 One size does not fit all: the promise of pharmacogenomics. Bethesda, MD: National Institutes of Health, 2007. Accessed March 5, 2007. http://www.ncbi.nlm.nih.gov/About/primer/pharm.html

2 Tucker G. Pharmacogenetics – expectations and reality. BMJ 2004;329:4-6.

3 Hopkins, MM, Ibarreta D, Gaisser S, et al. Putting pharmacogenetics into practice. Nat Biotechnol 2006;24(4):403-10.

4 Schmedders M, van Aken J, Feuerstein G, et al. Individualized pharmacogenetic therapy: a critical analysis. Community Genet 2003;6)2):114-9.

5 Hopkins, MM, Ibarreta D, Gaisser S, et al. Putting pharmacogenetics into practice. Nat Biotechnol 2006;24(4):403-10.

6 Personalized medicine: the emerging pharmacogenomics revolution. New York, NY: PricewaterhouseCoopers, 2005. Accessed April 25, 2006. http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf.

physicians to prescribe drugs and dosages in ways that are more likely to fit individual patient responses.

PGx also may help to improve the productivity of the new drug pipeline. The ability for PGx-based diagnostics to identify potentially high and low responders to investigational drugs may eventually improve the efficiency of clinical trials and lower their costs. The use of PGx in clinical trial design and patient accrual could lead to reductions in the time needed to develop a drug, from 10-12 years to perhaps as little as 3-5 years.[7] The ability to stratify patient groups using biomarkers and genomic data should enable discernment of significant treatment effects that would otherwise have been diluted in more heterogeneous populations. Also, this ability should enable development of drugs tailored for patients with rare or "orphan" conditions as well as other underserved patient groups. New methods for conducting clinical research have emerged and are being applied in PGx, such as the use of adaptive clinical trial designs. Such methods may help to improve and accelerate PGx research.[8,9,10,11]

In addition, PGx has the potential to improve treatments for chronic diseases, which pose the greatest disease and cost burdens in the US and other developed nations. The current therapeutic approach for these diseases is to slow their progression and diminish their symptoms. Along these avenues, the use of PGx may offer an opportunity to more dramatically reduce their burdens and improve the economic efficiency of the health system. Over time, PGx may help to reduce costs by curtailing the duration of illness through more effective treatments and minimizing the costs associated with ineffective treatment and avoidable ADRs.

A growing body of PGx knowledge involves interindividual genetic variations that result in variation in drug transporters, drug-metabolizing enzymes, and drug targets, all contributing to differences in how people respond to the same drugs. Greater understanding of the role of certain drug-metabolizing enzymes has broad potential for the health of large populations and subgroups. Prominent among these are cytochrome P450 (CYP450) and its variants, particularly CYP2D6 and CYP2C19, which play a role in the metabolism of approximately 25-30% of all prescription drugs.[12] The CYP2D6 enzyme metabolizes many of the most widely-prescribed drugs in the US for depression, cardiovascular disease, schizophrenia, attention-deficit hyperactivity disorder, prevention of nausea and vomiting for patients undergoing cancer chemotherapy, and symptoms of allergy and colds. It has differential effects among population subgroups, including that it is associated with slower drug metabolism among approximately 5-10% of Caucasians and 1-3% of Hispanics, African Americans and Asian Americans.[13]

Adaptation of regulatory and payment requirements is of particular importance to the future of PGx. FDA is clarifying the pathways from concept to market for PGx products with guidance and other documents pertaining to PGx data collection and submission and drug-device co-

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7 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

8 Roden DM et al. Pharmacogenomics: challenges and opportunities. Ann Intern Med 2006;145:749-57.

9 Gunderson KL, Kuhn KM, Steemers FJ, et al. Whole-genome genotyping of haplotype tag single nucleotide polymorphisms. Pharmacogenomics 2006;7(4):641-8.

10 Kuehn BM. Industry, FDA warm to "adaptive" trials. JAMA 2006;296(16):1955-7.

11 Gottlieb S. Speech before 2006 conference on adaptive trial design, Washington DC. Rockville, MD: US Food and Drug Administration, 2006. Accessed February 27, 2007. http://www.fda.gov/oc/speeches/2006/trialdesign0710.html.

12 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

13 Phillips KA, Van Bebber SL. Measuring the value of pharmacogenomics. Nat Rev Drug Discov 2005;4(6):500-9.

development. Also, diverse stakeholders in the field are building upon knowledge of ethical, legal and social issues, toward assuring protection of human research subjects, equity in access, patient confidentiality, duties to protect against adverse events, and protection of intellectual property. It will be important for these and other stakeholders to continually assess the environment for developing, validating, and delivering PGx diagnostics and therapies to ensure opportunities for PGx to yield health and economic benefits.

Genetic variation can be germline (inherited) or somatic (non-heritable, i.e., occurring over one's lifetime). Most PGx research to date has focused on germline variations. However, in many clinical conditions, the greater burden of disease arises from somatic variations, such as in cancerous tumors. This distinction in main pathways of genetic variation has implications for PGx research design, clinical and public health impact, resource allocation, and ethical, legal and social concerns.

While most of the current attention to PGx focuses on a small number of recent molecular breakthroughs, much of the potential health benefit of PGx resides in some of the longer-standing, wider-used products. Indeed, most ADRs, including many that are likely to be influenced by genotype, arise with use of older drugs. Much existing information on PGx for guiding available therapies appears to be ignored. A recent review of package insert information for the top 200 drugs prescribed in 2003 found that PGx data were available in the literature for 71.3% of these drugs, but that such information appeared in the package inserts of only a few of these drugs.[14] Much of the valuable information about PGx that is available remains to be put to work.

B. Challenges and Key Considerations

PGx faces many challenges. As described earlier, to date, only a small number of PGx products have reached the market and, of these, few have achieved adequate third-party reimbursement or widespread use in practice. The current health information infrastructure is not well-suited for developing PGx technologies and supporting informed practice at the site of care. PGx technologies are challenging the regulatory framework of FDA, and could outstrip it in certain ways. The agency's recent guidances applying to PGx do indicate clear moves toward effective regulatory adaptation. Federal agencies are moving to establish universal standards to enable interoperable health information technology systems that should facilitate product development and clinical efficiency. Current third-party payment mechanisms, and Medicare's in particular for screening, pose certain barriers to PGx innovation and can discourage adoption of PGx tests and therapies by providers. While PGx offers ways to improve care for broad populations and subgroups, advances in the field raise concerns about potential for disparities in access to care among underserved populations and breaches in protection of confidential genomic information, among others.

Key considerations for realizing the promise of PGx include the following:

- **Product development and clinical research** must be adapted to assess accuracy and predictive value of PGx-based diagnostics as well as biological markers, intermediate

[14] Zineh I, Pebanco GD, Aquilante CL, et al. Discordance between availability of pharmacogenetics studies and pharmacogenetics-based prescribing information for the top 200 drugs. Ann Pharmacother 2006;40(4):639-44.

endpoints, health outcomes and adverse events associated with PGx-based therapies in patient subgroups.

- **Regulation** of PGx products that fosters innovation while assuring patient safety and improved outcomes will require clear and evolving guidance from FDA and open, transparent communications with FDA staff.

- **Coverage and reimbursement** of new technologies, including PGx, are increasingly tied to evidence-based demonstration of clinical utility and value. A key reimbursement challenge that could affect industry's willingness to innovate is the prospect of payer resistance to the higher drug prices that may come with PGx-based targeted therapies.

- **Health information infrastructure** must be able to accommodate the types and level of detail of PGx-related data and provide interoperability to support PGx-based diagnostic and treatment decisions and surveillance.

- **Education and training** for physicians and other clinicians, including via on-site decision support tools, is essential to ensure competence with PGx technologies, the ability to counsel patients and families, and informed health care decisions.

- **Ethical, legal and social issues** will continue to arise as advances in PGx result in greater compilation, transmission, and use of genetic and genomic information of individuals and population subgroups. These must be addressed directly to ensure the confidence of the public, providers, industry, and policy-makers in advancing PGx, ensuring equitable access, and realizing its health and economic benefits.

C. Recommendations

Pursuant to these key considerations, SACGHS makes the following recommendations.

1) Basic Research

NIH should put more resources into basic research on the biochemical pathways associated with drug metabolism and drug action, on the genes and gene variations involved in these pathways, and on functions of those genes related to the safety and effectiveness of drug treatments.

2) Translational Research

As knowledge of the underlying biology accrues, further research will be needed to translate this knowledge into the development of clinically useful PGx technologies and to assess their clinical validity and clinical utility.

HHS agencies should facilitate the development of clinically useful PGx technologies by investing more resources into all components of translational research (both the translation of basic research findings into clinical trials as well as the translation of clinical research findings into clinical and public health practice and policy).

One of the foci of this translational research should be the development of more rapid, cost-effective genotyping technologies. To inform the development of point-of-care PGx tests, NIH should examine closely current efforts at CDC to develop point-of-care diagnostic tests to rapidly detect human cases of H5N1 avian influenza.

3) Clinical Trial Design

NIH should encourage sponsors and researchers to consult with FDA early in the study design phase so that study results can be used to support a pre-market review application. For example, studies should have sufficient statistical power, and quality controls should be in place.

NIH should also consider making FDA's quality-of-evidence standards a component of their assessments of the scientific merits of grant submissions.

4) Development and Co-development of PGx Products

A. FDA should build on its prior efforts to address the co-development of PGx drugs and diagnostics by developing a guidance document on this topic. FDA's guidance should clarify the review process for co-developed PGx products where the drug is subject to FDA review but the laboratory-developed companion diagnostic test may not be. It also should promote collaboration between drug and diagnostics manufacturers.

B. HHS should identify and provide incentives to the private sector to encourage the development of PGx products for smaller markets. Options to consider might include financial incentives, expedited FDA review, and greater intellectual property protection.

5) Analytic Validity, Clinical Validity, Clinical Utility, and Cost-Effectiveness

The adoption of PGx technologies will hinge on the availability of evidence of their analytic validity, clinical validity, clinical utility, and cost-effectiveness. The following steps should be taken to facilitate the establishment of the evidence base to support the integration of PGx technologies into clinical and public health practice.

A. HHS should provide resources to identify and address evidentiary gaps in the analytic validity, clinical validity, clinical utility, and cost-effectiveness of PGx.

   To better inform evidence-based decision-making, HHS should facilitate the development of tools to improve the validity of findings from observational studies. These tools include high-quality data resources; improved methodologies in the design, conduct and analysis of observational studies; and empirical research on the levels of evidence and types of studies required for making decisions for various purposes (e.g., coverage, clinical guidelines, performance metrics) and different clinical contexts.

B. HHS should initiate and facilitate collaborations between public (e.g., AHRQ, DVA, CDC, CMS, FDA, NIH) and private (e.g., private health insurance plans, pharmacy benefits managers, health care facilities with electronic medical records, clinical research databases

or genetic repositories) entities to advance the generation and sharing of knowledge on the analytic validity, clinical validity, clinical utility, and cost-effectiveness of PGx.

C. Drug and diagnostics manufacturers should conduct studies and disseminate results on the clinical validity and clinical utility of PGx (e.g., through publication in peer-reviewed journals), including statistically non-significant and negative findings. Alternately, manufacturers should make data publicly available to allow others to conduct and publish such studies.

   FDA can promote such studies by encouraging manufacturers to submit the data as part of their pre-market applications and post-market surveillance. FDA can facilitate the dissemination of results by listing published studies on its website (e.g., via its Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels).

D. NIH should provide mechanisms that promote interactions among basic, translational, clinical, and outcomes researchers for the identification of endpoints and data elements to be measured. The goal of these interactions would be to maximize the value and utility of basic and translational research data for downstream assessments of the clinical validity and clinical utility of PGx tests. NIH could facilitate such collaborations by adding field to the ClinicalTrials.gov database to identify clinical trials that could incorporate PGx study components.

6) Data Sharing and Database Interoperability

A. HHS should encourage private sector entities (including academic institutions) to voluntarily share proprietary data to advance the development and co-development of PGx products.

B. HHS should work with the private sector to identify obstacles to data sharing and to develop solutions to overcome these obstacles (e.g., legal and data confidentiality assurances, intellectual property protections).

C. Research, regulatory, medical record and claims databases need to be interoperable to facilitate research on PGx technologies and build the necessary evidence base. Interoperability of these databases will facilitate the study of the molecular pathogenesis of disease; the identification of targets for drug development; validation of PGx technologies; assessment of health outcomes associated with use of PGx technologies; and determination of the cost-effectiveness and economic impact of using these technologies.

   HHS and other relevant Departments (e.g., DVA, DOD) should work with the private sector to improve data sharing and interoperability among databases. Specifically, HHS should work with existing organizations to create uniform genomic data standards; explore ways to harmonize data analysis methodologies; and develop an infrastructure to enable data exchange. Comparable efforts to standardize phenotypic data are also needed.

D. FDA should identify, initiate and facilitate research opportunities and public/private partnerships to encourage the development and co-development of PGx products, e.g., through the Critical Path Initiative.

7) Protection of Personal Data

As data access and sharing expand, it will be important to strike the right balance between protecting the privacy and confidentiality of personal data and fostering access to these data for PGs research. Stronger data security measures may be needed as more PGx researchers access patient data.

8) Population Subgroup Differences in Drug Response

A. Because genomic factors may be more meaningful predictors of drug response than race and ethnicity categories, FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may better explain differences in drug response.

B. When drugs are shown to be effective in certain racial and ethnic subpopulations (e.g., BiDil), FDA should encourage manufacturers to conduct additional post-market studies to identify biological, social, behavioral and environmental markers that may underlie the differential drug response.

9) PGx-informed Prescription Drug Coverage

In instances where a validated PGx test is available to guide therapeutic decision-making, health plans, including Medicare prescription drug plans, should cover the most clinically appropriate drug as indicated by PGx test results.

10) Use of PGx Technologies in Clinical Practice

Health providers will need guidance how to use PGx information when making clinical decisions. The following steps will help ensure that PGx technologies are effectively integrated into clinical practice.

A. HHS should assist state and other Federal agencies and private sector organizations in the development, cataloguing and dissemination of case studies and practice models relating to the use of PGx technologies.

B. HHS should assist professional organizations in their efforts to help their membership achieve established competencies on the appropriate use of PGx technologies. HHS also should encourage and facilitate collaborations between the organizations and the Federal government around these activities.

C. As evidence of clinical validity and clinical utility for a PGx technology accrues, HHS should support the conduct of systematic reviews and technology assessments to summarize the evidence base. These systematic reviews and technology

assessments should be disseminated to professional organizations to facilitate the development of clinical practice guidelines.

D. FDA and drug and diagnostics manufacturers should focus more attention on ensuring that all relevant PGx information is included in drug and PGx test labels. The information contained in these labels should clearly describe the test's analytical validity and clinical validity and provide adequate and clear information for clinicians to use when making treatment decisions based on PGx test results (e.g., about dosing or drug selection).

E. NIH and FDA should continue expanding the Internet-based DailyMed project, which provides up-to-date, real-time prescription drug label/package insert information to people who have Internet access. To ensure that all sectors of the public have access to this information, FDA and NIH should develop other ways to disseminate this information.

11) Public Education and Engagement

A. HHS should use existing public consultation mechanisms to engage the public in a constructive dialogue regarding the potential benefits, risks and limitations of PGx technologies. This dialogue should include an assessment of their perceptions of and receptiveness to PGx and their willingness to participate in clinical research studies involving these technologies.

B. To inform the public about the availability, benefits, risks and limitations of PGx technologies, HHS should ensure that credible educational resources are widely available through Federal websites and other appropriate media.

12) Health Information Technology

A. The Office of the National Coordinator for Health Information Technology, through the activities of the American Health Information Community and in consultation with DVA and DOD, should take steps to ensure the inclusion of clinically validated PGx test results into patient records, along with decision support systems and tools to enhance appropriate test use and interpretation. Decision support systems and tools should include information about the availability of PGx tests, patients' test results, and relevant information for making treatment and dosing decisions.

B. Until electronic health record systems become a universal feature of the health care system, HHS should identify other ways to make best clinical practices for PGx more readily available to health providers as they are developed

13) Economic Value of PGx

To ensure that investments in PGx are well-spent, HHS should gather data to assess the economic value of investments in PGx relative to other health-related investments. This

assessment should encompass the cost-effectiveness of PGx technologies and take into account both the short- and long-term impacts on specific sectors and society as a whole.

14) ELSI Research

NIH, in collaboration with other agencies, should continue to encourage and fund research on the ethical, legal and social implications of PGx. This research should include studies of whether integration of PGx into clinical and public health practice exacerbates health and health care disparities, limits access to or decreases the quality of health care, increases medical liability, or results in genetic discrimination.

15) Coordination of PGx Activities

A. An interdepartmental work group should be established to review SACGHS's PGx recommendations, assess whether and how to implement them, monitor HHS's progress, and report back to SACGHS. The work group also could serve as a forum for discussion of other PGx activities.

B. HHS should assess the level and adequacy of resources being devoted to support the integration of PGx into clinical and public health practice to be sure gaps and opportunities identified in this report are addressed.

I. Introduction

The field of pharmacogenomics arises from the convergence of advances in pharmacology, genetics and, more recently, genomics. *Pharmacogenetics* is generally recognized as the study of how individual genetic differences affect drug response. In contrast, *pharmacogenomics* encompasses the role of the whole genome in pharmacology and drug design.[15,16,17] Even so, these terms are used inconsistently in the literature.[18,19,20,21] Many definitions of pharmacogenomics emphasize functional differences mediated by multigene interactions, as well as environmental interactions.[22,23,24,25,26,27] Other definitions broaden pharmacogenomics to include any variety of biomarker[28,29] or distinguish pharmacogenetics as the study and pharmacogenomics as the application.[30,31] Some scientists who consider there to be little meaningful difference between the two terms are using the terms interchangeably.

In the present document, the term "pharmacogenomics" (PGx) refers to the study of how differences in gene expression affect an individual's response to drugs. This encompasses differences in DNA sequences related to an individual's metabolism of drugs (pharmacokinetics) or physiological response to drugs (pharmacodynamics). Pharmacogenomic tests frequently employ high throughput technologies, such as microarrays or "gene chips," that allow for the analysis of whole genomes or specific candidate genes or biomarkers for alterations in gene expression affecting drug action or activity.

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20 Resolution of the Secretary's Advisory Committee on Genetics, Health, and Society on genetics education and training of health professionals. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, 2004. Accessed August 15, 2006. http://www4.od.nih.gov/oba/sacghs/reports/EducationResolutionJune04.pdf.

21 Resolution of the Secretary's Advisory Committee on Genetics, Health, and Society on genetics education and training of health professionals, 2004.

22 Goodman C, Faulkner E, Gould C, et al. The value of diagnostics: innovation, adoption, and diffusion into health care. Washington, DC: The Advanced Medical Technology Association, 2005. http://www.advamed.org/publicdocs/thevalueofdiagnostics.pdf.

23 Shastry BS 2006.

24 A roadmap for the integration of genetics and genomics into health and society, 2004.

25 Personalised medicines: hopes and realities. London, England: The Royal Society, 2005. Accessed April 25, 2006. http://www.royalsoc.ac.uk/displaypagedoc.asp?id=15874.

26 Pharmacogenetics: ethical and regulatory issues in research and clinical practice. Report of the Consortium on Pharmacogenetics, findings and recommendations. Minneapolis, MN: University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics, 2002. Accessed April 25, 2006. http://www.bioethics.umn.edu/news/pharm_report.pdf.

27 Guidance for industry: pharmacogenomic data submissions. Rockville, MD: US Food and Drug Administration, 2005. Accessed May 2, 2006. http://www.fda.gov/cber/gdlns/pharmdtasub.htm.

28 Goodman C 2005.

29 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

30 Pharmacogenetics: towards improving treatment with medicines. Geneva, Switzerland: Council for International Organizations of Medical Sciences, 2005.

31 Melzer D 2003.

A. The Role of PGx in Addressing Unmet Health Needs

Increasing demands for improved health and quality of life are prompting changes in the US health care system.[32,33] While health care needs in the US are well-documented, the means for meeting these challenges vary and have had mixed success.[34,35,36] PGx is a promising, yet still emerging, avenue for addressing a number of unmet health care needs. As demonstrated in its initial clinical applications to date, PGx can provide clinicians with tools to assess risks and benefits of using available medicines for particular patients and select therapies and treatment plans that are tailored for those patients.[37,38]

PGx has the potential to enable a new paradigm of personalized medicine, extending primary and secondary prevention and delivering the correct drug at the correct dosage to the correct patient at the correct time.[39,40,41,42] Still, realizing the benefits of PGx on a large scale is a long-term goal.

1) Short-term Benefits of PGx

Incorporating PGx into health care offers potential opportunities to improve patient health and safety through reducing adverse drug reactions (ADRs) and improving drug effectiveness. Some of the new benefits arising today suggest broader potential for gains in health care quality and outcomes.

a) Improved Patient Safety

The current "trial and error" clinical practice model contributes to nearly three million incorrect or ineffective drug prescriptions annually.[43] In 2001 alone, ADRs affected approximately 2.2 million people, accounting for as many as 106,000 deaths and ranking between the fourth and sixth leading cause of death in the US. The economic burden associated with ADRs is substantial, with estimated annual costs earlier this decade exceeding $177 billion.[44,45,46] ADRs are the leading cause of market withdrawals of drugs.[47]

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32 Snyderman R, Williams RS. Prospective medicine: the next health care transformation. Acad Med 2003;78(11):1079-84.

33 Cutler DM, McClellan M. Is technological change in medicine worth it? Health Affairs 2001;5:11-29.

34 McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. N Engl J Med 2003;348(26):2635-45.

35 Crossing the quality chasm: a new health system for the 21st century. Washington, DC: Institute of Medicine, National Academies Press, 2001. Accessed May 5, 2006. http://www.nap.edu/books/0309072808/html.

36 Priority areas for national action: transforming health care quality. Washington, DC: Institute of Medicine, National Academies Press, 2003. Accessed May 5, 2006. http://www.nap.edu/books/0309085438/html/.

37 Hopkins, MM, Ibarreta D, Gaisser S, et al. Putting pharmacogenetics into practice. Nat Biotechnol 2006;24(4):403-10.

38 Schmedders M, van Aken J, Feuerstein G, et al. Individualized pharmacogenetic therapy: a critical analysis. Community Genet 2003;6)2):114-9.

39 Melzer D, Raven A, Detmer DE, et al. My very own medicine: what must I know? Information policy for pharmacogenetics. Cambridge, UK: University of Cambridge, Department of Public Health and Primary Care, 2003.

40 Coverage and reimbursement of genetic tests and services. Washington, DC: United States Department of Health and Human Services, Secretary's Advisory Committee on Genetics, Health, and Society, 2006. Accessed April 25, 2006. http://www4.od.nih.gov/oba/sacghs/reports/CR_report.pdf.

41 Personalised medicines: hopes and realities, 2005.

42 Ginsburg GS, Angrist M. The future may be closer than you think: a response from the Personalized Medicine Coalition to the Royal Society's report on personalized medicine. Future Medicine 2006;3(2):119-23.

43 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

44 Ernst FR 2001.

45 To err is human: building a safer health system, 2000.

Few prescribed medications are effective for all who use them, and most ADRs are caused by an exaggerated effect of a drug on the body.[48,49] Drug effectiveness can be influenced by genetically-mediated variations that affect the metabolism, transport, distribution, absorption and excretion of the drug.[50] Genetic variations of drug-metabolizing enzymes are highly correlated with ADRs.[51] One of the most anticipated potential benefits of PGx diagnostics is the reduction of ADRs. *In vitro* diagnostic tests used in PGx identify individuals more likely to experience ADRs from particular drugs because of genetic variations in drug targets in the body or in the enzymes that metabolize drugs. Achieving even modest reductions in the rate of ADRs could result in substantial improvements in health care outcomes and costs.

One of the drug-metabolizing enzymes that figures prominently in contemporary and future PGx applications is known as CYP2D6. This enzyme metabolizes many of the most widely-prescribed drugs in the US, including Paxil (paroxetine), Effexor (venlafaxine), Prozac (flouxetine), Toprol (metoprolol), Risperidal (risperidone), Adderall (amphetamine/dextroamphetamine), Inderal (propranolol), Coreg (carvedilol), Zofran (ondansetron), Strattera (atomoxetine), and Tussionex (chlorpheniramine and hydrocodone).[52] A variant of the CYP2D6 gene is associated with slower metabolism of these drugs and occurs with varying rates among population groups. The prevalence of the CYP2D6 variant is estimated at 5-10% among Caucasians and 1-3% among Hispanics, African Americans and Asian Americans. As is the case with similar genetically determined metabolic traits, conventional racial and ethnic designations are inadequate markers for genetically determined metabolic traits that are present across many population groups and that can be more accurately identified using PGx testing.

b) Increased Effectiveness of Care

Varying response rates to drug treatments pose clinical and economic concerns. Of 14 major drug classes, seven have shown effective patient response rates of less than 50%.[53,54] Common treatments for diseases, including diabetes, depression, and asthma, are effective for only approximately 60% of the patients that are prescribed medication, while prescribed cancer treatments are effective in only 25% of cancer patients.[55]

While current methods of "trial and error" prescribing for determining the appropriate drug and dosage for particular patients is adequate and minimally harmful for many drugs, they can be inefficient, expensive, and occasionally detrimental to patient health. Some PGx diagnostics

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46 Lazarou J 1998.

47 Gud J, Bagatto D. Theragenomic knowledge management for individualized safety of drugs, chemicals, pollutants and dietary ingredients. Expert Opin Drug Metal Boxicol 2005;1(3):537-54.

48 Pharmacogenetics: ethical issues. London, England: Nuffield Council on Bioethics, 2003. Accessed April 25, 2006. http://www.nuffieldbioethics.org/fileLibrary/pdf/pharmacogenetics_report.pdf.

49 Phillips KA, Veenstra DL, Oren E, et al. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. JAMA 2001;286;2270-9.

50 Personalised medicines: hopes and realities, 2005.

51 Phillips KA 2001.

52 Phillips KA 2005.

53 Garrison LP Jr, Austin MJ. Linking pharmacogenetics-based diagnostics and drugs for personalized medicine. Health Affairs 2006;25(5):1281-1290.

54 Spear BB, Health-Chiozzi M, Fugg J. Clinical application of pharmacogenetics. Trends Mol Med 2001;7(5):201-204.

55 Spear BB 2001.

may circumvent such "trial and error" prescribing by stratifying patients by their risk for ADRs and likelihood of drug response and treating them accordingly.[56,57,58]

2) Long-term Benefits of PGx

Among the potential long-term benefits of PGx are reducing the burden of disease, improving the economic efficiency of the health care system, and reducing some disparities in health care access and outcomes.

a) Reduced Burden of Disease

Chronic conditions are a growing concern in the US. More than 134 million Americans are expected to have chronic conditions by 2020.[59] PGx is emerging as a means for managing variation in individual drug response in such chronic and complex disease areas as cancer, cardiovascular disease, asthma and HIV/AIDS.[60,61,62,63,64] Current medical treatments aim to slow disease progression and reduce symptoms, where breakthroughs in biotechnology can reduce the actual burden and prevalence of disease.[65]

Effective treatments for many chronic conditions are grossly underutilized. Half of patients with chronic health conditions discontinue use of their medications after one year.[66] Rational therapy selection using PGx could diminish some compliance problems and increase treatment effectiveness, as well as yield economic benefits to consumers, payers, and the broader health care system.

b) Increased Economic Efficiency to the Health Care System

The current US health care system tends to align toward short-term problems rather than investing in care that can be economically efficient in the long-term. Health care spending continues to increase faster than the economy at large, with little improvement in health care quality. Greater use of validated preventive services and an increase in translational research focused on improving the effectiveness and efficiency of health care delivery could contribute to a more efficient system.[67]

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56 Pharmacogenetics: ethical issues, 2003.

57 Beitelshees AL, McLeod HL. Applying pharmacogenomics to enhance the use of biomarkers for drug effect and drug safety. Trends Pharmacol Sci 2006;27(9):498-502.

58 Pharmacogenetics: ethical issues, 2003.

59 Crossing the quality chasm: a new health system for the 21st century, 2001.

60 Chasman DI, Posada D, Subrahmanyan L, et al. Pharmacogenetic study of statin therapy and cholesterol reduction. JAMA 2004;291(23):2821-7.

61 Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352(10):997-1003.

62 Esteva FJ, Cheli CD, Fritsche H, et al. Clinical utility of serum HER2/neu in monitoring and prediction of progression-free survival in metastatic breast cancer patients treated with trastuzumab-based therapies. Breast Cancer Res 2005;7(4):R436-43.

63 Szefler SJ, Apter A. Advances in pediatric and adult asthma. J Allergy Clin Immunol 2005;115(3):470-7.

64 Rotger M, Colombo S, Furrer H, et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. Pharmacogenet Genomics 2005;15(1):1-5.

65 Teutsch SM, Berger ML. Misaligned incentives in America's health: who's minding the store? Ann Fam Med 2005;3:485-7.

66 Teutsch SM 2005.

67 Teutsch SM 2005.

Personalized medicine may reduce health care costs over the long-term by diminishing the duration of illness and the costs associated with ineffective treatment and avoidable ADRs.[68] Even with these benefits, the average consumer likely will experience a net increase in drug costs, particularly in the short-term, due to adoption of new PGx drugs and technologies and greater burden of patient cost sharing for drugs.[69,70] Providers will face additional costs of education and an increase in the amount of time needed to use and interpret diagnostic results.

PGx may result in cost savings via testing patients for potential ADRs or ineffective drug responses. Payers' willingness to invest in this testing may be limited by short-term costs of PGx adoption and the inability to realize the long-term returns on many preventive measures, given high rates of health plan enrollee turnover.[71] Such testing may not be cost effective for some patient conditions generated by more complex, polygenic interactions.[72] Storage of laboratory samples and genetic information for later use could lower some of these costs.

PGx diagnostics can also improve economic efficiency by speeding the selection of an effective drug therapy and improving the efficacy of selected drugs through appropriate dosing schedules. PGx tests may help clinicians identify who is the best candidate for a treatment and who will respond fully to a treatment, potentially eliminating unnecessary treatment for those who have an unfavorable risk-benefit ratio.[73]

c) Enhanced Patient Access and Improved Health Outcomes

The current health care system is poorly suited to deal with fundamental problems of access to appropriate care.[74] Landmark studies conducted in recent years by RAND demonstrate that patients received only 55% of recommended care for their conditions. There were significant though moderate differences among sociodemographic groups, e.g., women vs. men, younger vs. older adults, blacks and Hispanics vs. whites, and higher- vs. lower-income groups. However, the researchers observed that such differences were small in comparison to the gap for each subgroup between observed and recommended care.[75,76]

The cause of disparities in access to health care have far more to do with socioeconomic factors than the lack of targeted therapies, and improvements in health outcomes will be greater through interventions directed at addressing these socioeconomic factors. Nonetheless, PGx applications may make a contribution as well. Some observers suggest that PGx tools will enable more cost-effective development of drugs using patient subgroups in clinical trials that are more likely to respond to investigational drugs, providing more targeted labeling of patient indications for use in practice. Doing so may allow industry to develop and market drugs in

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68 Bartfai T. Pharmacogenomics in drug development: societal and technical aspects. Pharmacogenomics J 2004;4: 226-32.

69 Pharmacogenetics: ethical issues, 2003.

70 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

71 Phillips KA, Van Bebber SL. A systematic review of cost-effectiveness analyses of pharmacogenomic interventions. Pharmacogenomics 2004;5(8):1139-49.

72 Personalised medicines: hopes and realities, 2005.

73 Garrison LP Jr 2006.

74 Teutsch SM 2005.

75 McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. N Engl J Med 2003;348(26):2635-45.

76 Asch SM, Kerr EA, Keesey J, et al. Who is at greatest risk of receiving poor-quality health care? N Engl J Med 2006;354(11):1147-56.

instances that would otherwise yield insufficient returns on investment.[77] If this model prevails, including availability of sufficient payment for these drugs, some underserved populations could experience greater access to drugs that are safer and more effective.

B. Complexity of the Science

A growing body of PGx knowledge involves interindividual genetic variation that results in variation of drug transporters, metabolizing enzymes and drug targets, leading ultimately to variation in drug response.[78,79] Genetic variation can be germline (inherited) or somatic (non-heritable). Somatic variations arise during one's lifetime, a result of environmental or behavioral factors, and can be identified in tumor tissue or other patient samples. Most PGx research to date has focused on germline variations; however, in many forms of clinical conditions, the significant burden of disease arises from somatic variations.[80] This distinction in two main pathways of genetic variation has implications for PGx research design, clinical and public health impact, and resource allocation.[81]

The scientific goal of PGx is to identify and quantify the association between variations in DNA sequence and/or structures with variations in the drug response phenotype, i.e., the "genotype-phenotype correlation." A drug acts on a patient, but the patient's body acts also on the drug. It must be absorbed, arrive at its site of action, interact with its targets, and be metabolized and excreted. Pharmacokinetics influences the concentration of a drug as it arrives at its target, predominantly through drug metabolizing enzymes. Pharmacodynamics refers to the factors that influence the response of the target itself and all the downstream signaling that comes from the target. All of these processes can be subject to clinically relevant genetic variation.[82]

PGx can be used to determine a patient's metabolic response to particular types of drugs, which is influenced by drug-metabolizing enzymes that are mediated by individual genetic variations (polymorphisms and insertions/deletions). Prominent among these are cytochrome P450 (CYP450) and its variants, particularly CYP2D6 and CYP2C19, which play a role in the metabolism of approximately 25% of all prescription drugs.[83]

A prototypic example of applied PGx is a test that predicts patient response to thiopurine 6-mercaptopurine, a mainstay drug used in a protocol to treat acute lymphoblastic leukemia (ALL) in children. The drug is metabolized by the enzyme thiopurine methyltransferase (TPMT); however, individuals who have a germline variation, resulting in low TPMT activity, are at serious risk for life-threatening myelosuppression upon treatment with the drug. Due to decreased levels of enzyme production, the concentration of this drug in the bloodstream of these individuals can increase to toxic levels. Before knowledge of this variation and myelosuppression, a child being treated for ALL was at risk for an adverse event that destroys

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77 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

78 Evans WE, Relling MV. Moving towards individualized medicine with pharmacogenomics. Nature 2004;429(6990):464-8.

79 Shastry BS 2006.

80 Our inheritance, our future: realising the potential of genetics in the NHS. London, England: National Health Service, 2003. Accessed March 2, 2007. http://www.dh.gov.uk/assetRoot/04/01/92/39/04019239.pdf.

81 Baker SG, Kaprio J. Common susceptibility genes for cancer: search for the end of the rainbow. BMJ 2006;332(7550):1150-2.

82 Pharmacogenetics: ethical issues, 2003. .

83 Jain KK. Applications of AmpliChip CYP450. Mol Diagn 2005;9(3):119-27.

the bone marrow and leads to death. Testing now allows identification of TMPT variants, thus avoiding the risk of this life-threatening adverse event.[84]

An application of PGx related to pharmacodynamics is targeting drug therapy based on somatic variations occurring at drug target sites. An example for such a PGx application is the cancer therapy Herceptin.[85] In 25-30% of women with metastatic breast cancer, there is an overexpression of HER2/neu oncogenes associated with genetic alterations in specific cell types. PGx tests are available to identify women whose tumors have HER2 protein overexpression. These women show better response to Herceptin, allowing targeted drug therapy.

In addition to genetic variation, physicians who prescribe medications understand that other factors influence variation in drug response. These factors include age, sex, diet, other underlying medical conditions, and drug interactions. Warfarin, a commonly prescribed drug for those at risk for harmful blood clots, is a drug with complex factors affecting proper dosing. Warfarin blocks the Vitamin K pathway, which is required to make active clotting factors. CYP2C9, another cytochrome P450, metabolizes S-warfarin. If an individual is homozygous for the *3 variant of the gene, clearance of this drug is greatly reduced. Warfarin action is also affected by the gene Vitamin K oxidoreductase C1, or VKORC1. The optimal maintenance doses of warfarin can vary two-fold depending whether an individual has two copies of the low dose VKORC1 variant or two copies of the high dose variant. Variants in VKORC1 are reported to be responsible for about 30% of the variation in the final warfarin dose, with CYP2C9 responsible for about 10%.[86]

C. Current State of the PGx Field

In the 1990s, a widely held vision of PGx innovation promised a new paradigm in health care. Although a small number of important PGx products have reached the market, these early expectations for the field have not yet been realized. While the push for innovation and demand for truly personalized medicine remain, new products face careful assessments of benefits, risks and costs. While some PGx products and services are available in the health care market, their clinical use has been limited by a lack of evidence of clinical validity and utility and other barriers.[87] A test has clinical validity if it accurately and reliably differentiates patients based on the actual presence or level of a risk factor, condition or disease; predicts response to treatment; or predicts health outcomes. A test has clinical utility if the use of the test results (e.g., via informing treatment or patient management decisions) leads to improved patient outcomes.

Approaches to regulation and reimbursement will need to account for the ways in which PGx technologies are used, including the complementary relationship of particular combinations of tests and therapies. Tracking the impact of PGx on disease burden and quality of life is also needed to inform public health decisions. In the clinical setting, more guidance based on clinical outcomes data is needed, including precise dosing recommendations. In addition, enhancements

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84 Personalised medicines: hopes and realities, 2005.

85 About Herceptin. South San Francisco, CA: Genentech, Inc., 2006. Accessed June 7, 2006. http://www.herceptin.com/herceptin/patient/about/herceptin.jsp.

86 Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med 2005;352(22):2285-93.

87 Webster A, Martin P, Lewis G, Smart A. Integrating pharmacogenetics into society: in search of a model. Nat Rev Genet 2004;5(9):663-9.

in post-marketing surveillance methods can generate information about benefits, risks and costs of PGx products. However, current post-marketing surveillance techniques and infrastructure may be inadequate for the collection and analysis of such data.[88,89,90]

PGx offers certain alternatives to traditional models of drug development, regulation, clinical practice and reimbursement. The prevailing blockbuster model of developing drugs for broad populations, intended to yield annual revenues exceeding $1 billion, is strained due to increases in the time and costs of drug development, rising prices of prominent or truly novel ("breakthrough") drugs, and heightened public awareness of actual or perceived breaches in drug safety.[91] Using PGx-related technologies for drug development can shift the focus to stratified populations and segmenting formerly large target populations. New methods for conducting clinical research have also emerged and are being applied in PGx, such as adaptive clinical trial designs.[92,93,94,95] The resulting PGx-related drugs and test combinations are likely to come with high sticker prices, although these prices may be offset by downstream reductions in inappropriate drug use, fewer visits to physicians to change medications or adjust dosages, and cost savings realized from decreased ADRs. The prospect of still-daunting drug development costs and narrower markets for new drugs could provide further motivation for manufacturers to affix premium prices to these drugs.

While most of the current attention on PGx focuses on a small number of recent molecular breakthroughs, much of the potential health benefit of PGx resides in some of the longer-standing, widely used products. Certainly, most ADRs, including many that are likely to be influenced by genotype, arise with use of older drugs.[96] Much existing information on PGx that could be used to guide available therapies appears to be ignored. Instructive of missed opportunity is a recent review of package insert information for the top 200 drugs prescribed in 2003, which found that PGx data were available in the literature for 71% of these drugs. In a third of these instances, the literature reported that the gene involved coded for a drug metabolizing enzyme, while the remaining two-thirds contained information related to genetic variability in target proteins and drug transporters. However, only 3 drugs among the 200 had package inserts with PGx prescribing information that was deemed to be useful to guide therapy: celecoxib (Celebrex), fluoxetine (Prozac), and pantoprazole (Protonix). Further, there was no consensus on the strength of association between genetic variability and drug response for these agents. These

88 Melzer D 2003.

89 About MedWatch. Rockville, MD: US Food and Drug Administration, 2003. Accessed April 26, 2006. http://www.fda.gov/medwatch/What.htm.

90 Transcript of ninth meeting - March 27, 2006. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, 2006. Accessed May 4, 2006. http://www4.od.nih.gov/oba/SACGHS/meetings/March2006/transcripts/FullDayTranscript03-27.pdf.

91 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

92 Roden DM et al. Pharmacogenomics: challenges and opportunities. Ann Intern Med 2006;145:749-57.

93 Gunderson KL, Kuhn KM, Steemers FJ, et al. Whole-genome genotyping of haplotype tag single nucleotide polymorphisms. Pharmacogenomcs 2006;7(4):641-8.

94 Kuehn BM. Industry, FDA warm to "adaptive" trials. JAMA 2006;296(16):1955-7.

95 Gottlieb S. Speech before 2006 conference on adaptive trial design, Washington DC. Rockville, MD: US Food and Drug Administration, 2006. Accessed February 27, 2007. http://www.fda.gov/oc/speeches/2006/trialdesign0710.html.

96 Melzer D, Raven A, Ling T, Detmer D, Zimmern R. Pharmacogenetics: policy needs for personal prescribing. J Health Serv Res Policy 2005;10(1):40-4.

findings suggest that much of the available PGx data in the literature is ignored in prescribing information included in package inserts.[97]

D. Purpose and Scope of This Report

The purpose of this report is to explore the opportunities for PGx to advance the development of diagnostic, therapeutic, and preventive strategies to improve health and to identify challenges to the integration and application of PGx to clinical practice and public health. The report addresses the current and evolving environment for PGx and its potential to inform the decisions of clinicians, policymakers and other stakeholders. It is intended to provide policy-focused background information on PGx to help frame recommendations to the Secretary and other policy-makers and stakeholders.

In order to highlight the steps in the process from innovation to adoption and diffusion of PGx, this report is organized into three main sections. The first, ***Research and Development***, provides an overview of basic, translational and clinical research for PGx and describes aspects of the infrastructure needed to promote research and development (R&D). ***Gatekeepers*** identifies four main types of health care stakeholders involved in facilitating the progression of PGx, from R&D to the marketplace. ***Implementation of PGx to Improve Outcomes in Clinical and Public Health Practice*** explores important aspects of using PGx in clinical practice, including such issues as the need for education and information technology to support PGx. Ethical, legal and social issues related to PGx are described throughout the report. Although the path from innovation to adoption and diffusion of health care technology is traditionally described as linear, the major phases along this continuum overlap, and there are points at which information learned in one phase helps to inform a future phase. As PGx technologies are implemented in clinical practice, lessons learned may inform priorities for future R&D. These points of critical feedback are also noted throughout the report.

[97] Zineh I 2006.

II. Research and Development

PGx has multiple potential roles along the R&D continuum. In addition to providing more accurate diagnostic information to inform safer and more effective drug selection and dosing, it can contribute to prevention through improved health outcomes, and quality of life.[98,99] The following sections describe the potential role PGx can play throughout the R&D process, an overview of the infrastructure needed to promote and support the role of PGx in R&D, and potential ethical, legal, and social considerations arising from PGx-based R&D.

A. Basic Research

Basic research in PGx primarily involves the identification of the biochemical pathways and related biomarkers involved in drug metabolism and drug response that can be applied in clinical research. A major component of this basic PGx research is focused on identifying single nucleotide polymorphisms (SNPs) that serve as biomarkers of individual variation. For example, the CYP450 enzymes noted above are involved in the metabolism of 25-30% of currently available drugs and are highly polymorphic.[100] SNPs are inherited in blocks, and therefore can serve as a proxy for sequencing the full gene and detecting variation, a more expensive and time-consuming endeavor. In addition to identifying relevant biomarkers, much effort in basic PGx research is devoted to refining and improving the sensitivity of the high-throughput methods for detecting gene expression and drug response.

Genome-wide association studies as well as candidate gene studies are emerging as useful tools for the discovery of gene-loci specific variability in drug response. Genome-wide association studies are defined as any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition.[101] Since genome-wide association studies collect large volumes of genotypic and phenotypic information, researchers may be able to determine correlations between a certain genetic makeup and disease status. These correlations may lead investigators to a series of potential genetic targets or "candidate genes", which can then be tested for drug response or efficacy in both *in vitro* and *in vivo* models.

Efforts currently underway to elucidate these associations include the International HapMap Consortium, Genetic Association Information Network (GAIN), Genes and Environment Initiative (GEI), and Framingham Genetic Research study. The International HapMap Consortium aims to develop a human haplotype map (the HapMap) to describe these patterns of variation in the human genome.[102] GAIN is a public-private partnership of NIH, the Foundation for NIH, and Pfizer Global Research and Development to fund whole genome association studies and genotyping services to aid in the identification of genetic risk

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98 Issa AM. Ethical perspectives on pharmacogenomic profiling in the drug development process. Nature 2002;1:300-8.

99 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

100 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

101 Genome-Wide Association Studies. Bethesda, MD: National Institutes of Health, 2007. Accessed March 21, 2007. http://grants.nih.gov/grants/gwas/index.htm.

102 International HapMap Project. Coldspring Harbor, NY: International HapMap Consortium, 2007. Accessed March 2, 2007. http://www.hapmap.org/

factors.[103,104] GEI will provide genotyping facilities, a coordinating center for analytic support, data quality assessment and quality control, logistical management, and support for the investigation of major scientific questions using existing DNA samples from well-characterized subjects for genome-wide association studies. Data for this research will be made available in the central, controlled-access database established by the National Center for Biotechnology Information (NCBI).[105] In the Framingham Genetic Research Study, 9,000 subjects from the Framingham Heart Study will be involved in genome-wide association studies to identify critical genetic variations underlying cardiovascular disease and other chronic diseases.[106]

Although genome-wide association studies can be a useful tool for PGx research, the associations between loci are complex.[107,108] Uncertainty remains over the robustness of genome-wide association studies, including concerns over sample size, collection bias and the current ability of high-throughput technologies to produce the necessary volume of data.[109,110] Thus, while these methods may still have considerable value in scientific discovery, routine clinical applicability that involves affordable sequencing and storing of whole genomes still remains far in the future. The sequencing and use of whole genomes for medical decision making may not be available for another 5 to 10 years and will require robust information management systems and methods for genomic analysis.[111] Some have also pointed to an essential need for more cost-effective genotyping methods in genome-wide association studies.[112,113]

Recommendation 1

NIH should put more resources into basic research on the biochemical pathways associated with drug metabolism and drug action, on the genes and gene variations involved in these pathways, and on functions of those genes related to the safety and effectiveness of drug treatments.

103 Genetic Association Information Network. Bethesda, MD: National Institutes of Health, 2007. Accessed March 7, 2007. http://www.fnih.org/GAIN/GAIN_home.shtml.

104 Genetic association information network launched: novel public-private partnership created to unravel the genetics of common disease through whole genome association studies. Perlegen Sciences News Release February 8, 2006. Mountain View, CA: Perlegen Sciences. Accessed March 7, 2007. http://www.perlegen.com/newsroom/pr/2006/2006_02_08_Pfizer_NIH_Press%20Release.pdf

105 The Genes and Environment Initiative (GEI). Bethesda, MD: National Institutes of Health, 2006. Accessed March 7, 2007. http://www.gei.nih.gov/.

106 NHLBI launches Framingham genetic research study. FYI from the NHLBI 2006;7(1). Bethesda, MD: National Institutes of Health, 2006. Access March 7, 2007. http://www.nhlbi.nih.gov/public/may06/feature.htm#fram

107 Roden DM et al. Pharmacogenomics: challenges and opportunities. Ann Intern Med 2006;145:749-57.

108 Gunderson KL, Kuhn KM, Steemers FJ, et al. Whole-genome genotyping of haplotype tag single nucleotide polymorphisms. Pharmacogenomcs 2006;7(4):641-8.

109 Wang WY, Barratt BJ, Clayton DG, Todd JA. Genome-wide association studies: theoretical and practical concerns. Nature Review Genetics 2005;6(2):109-18.

110 Farrall M, Morris AP. Gearing up for genome-wide gene-association studies. Human Molecular Genetics 2005;14(R2):R157-62.

111 Roden DM et al. Pharmacogenomics: challenges and opportunities. Ann Intern Med 2006;145:749-57.

112 Gunderson KL, Kuhn KM, Steemers FJ, et al. Whole-genome genotyping of haplotype tag single nucleotide polymorphisms. Pharmacogenomcs 2006;7(4):641-8.

113 Goldstein DB. The genetics of human drug response. Philos Trans R Soc Lond B Biol Sci 2005:29;360(1460):1571-2.

B. Translational Research: From Basic to Clinical Research

The term "translational research" can be used to describe translation at different phases of R&D. Various models depict translational research as a process occurring in two stages.[114,115,116] The first, sometimes referred to as type 1 (T1) translation, uses the findings from basic research, including preclinical studies, to inform the development and testing of an intervention in clinical trials, such as phase I-III clinical trials. The second, type 2 (T2) translation, involves the translation of findings from clinical research into clinical and public health practice and policy.[117,118]

The National Cancer Institute's Early Detection Research Network (EDRN) is an example of a program that aims to encourage and accelerate the translation of basic research into clinical research. The program facilitates the development, testing and assessment of promising biomarkers and technologies as well as assessment of existing, proven ones.[119] Its work products include a list of common data elements; standard operating procedures for assays; methods and protocols for collection and processing of biological samples; other reference materials to assist investigators to conduct experiments in a consistent, reliable manner; and tools for the collection, classification, storage, and analysis of information, enabling access to and sharing of data among multiple organizations.[120] EDRN also fosters collaboration among academic and industry stakeholders in a range of fields and promotes rapid dissemination of information.[121] Researchers outside of EDRN are provided opportunities to collaborate with EDRN investigators to use shared resources through the network, such as new technologies, specimens, high-risk registries, and cohorts, or to seek funding for validation studies.[122]

The Pharmacogenetics Research Network (PGRN) is a similar effort led by the National Institute of General Medical Sciences (NIGMS). PGRN is a multi-disciplinary network intended to translate pharmacogenetic information into safe and effective drug therapies designed for individual patients. This nationwide collaboration of 12 independently funded interactive research groups studies the relationship between genetics and patient drug response. In the past five years, PGRN scientists have explored the effect of genetics on medications for diseases such as asthma, depression, cancer and heart disease. A major component of PGRN is the Pharmacogenomics Knowledge Base (PharmGKB), where pharmacogenetics data from PGRN are stored and freely available for scientists and researchers. With data on more than 10,000

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114 Sussman S, Valente TW, Rohrbach LA, et al. Translation in the health professions: converting science into action. Eval Health Prof 2006;29(1):7-32.

115 Westfall JM, Mold J, Fagnan L. Practice-based research--"Blue Highways" on the NIH roadmap. JAMA 2007;297:403-6.

116 Ozdemir V, Williams-Jones B, Cooper DM, et al. Mapping translational research in personalized therapeutics: from molecular markers to health policy. Pharmacogenomics 2007;8(2):177-85.

117 Sussman S, Valente TW, Rohrbach LA, et al. Translation in the health professions: converting science into action. Eval Health Prof 2006;29(1):7-32.

118 Westfall JM, Mold J, Fagnan L. Practice-based research--"Blue Highways" on the NIH roadmap. JAMA 2007;297:403-6.

119 Objectives - Early Detection Research Network. Rockville, MD: National Cancer Institute, Division of Cancer Prevention, Early Detection Research Network, 2006. Accessed December 4, 2006. http://edrn.nci.nih.gov/about-edrn/objectives/.

120 Resources. Rockville, MD: National Cancer Institute, Division of Cancer Prevention, Early Detection Research Network, 2006. Accessed December 4, 2006. http://edrn.nci.nih.gov/edrn/resources.

121 Objectives - Early Detection Research Network, 2006.

122 Collaborative opportunities - Early Detection Research Network. Rockville, MD: National Cancer Institute, Division of Cancer Prevention, Early Detection Research Network, 2007. Accessed February 27, 2007. http://edrn.nci.nih.gov/colops/.

human gene variations that affect drug response, this network enables access of the scientific community to information on genes, drugs and diseases.[123]

As described in Section C, *Infrastructure Enabling Research and Development,* databases and repositories that store PGx data are expected to play a role in translating basic research into clinical research. PGx databases should enable more efficient clinical trial enrollment by stratifying potential participants by particular markers and potential responsiveness to an investigational drug.[124]

Recommendation 2

As knowledge of the underlying biology accrues, further research will be needed to translate this knowledge into the development of clinically useful PGx technologies and to assess their clinical validity and clinical utility.

HHS agencies should facilitate the development of clinically useful PGx technologies by investing more resources into all components of translational research (both the translation of basic research findings into clinical trials as well as the translation of clinical research findings into clinical and public health practice and policy).

One of the foci of this translational research should be the development of more rapid, cost-effective genotyping technologies. To inform the development of point-of-care PGx tests, NIH should examine closely current efforts at CDC to develop point-of-care diagnostic tests to rapidly detect human cases of H5N1 avian influenza.

C. Clinical Research

Findings from PGx-informed basic and translational research can affect the design of clinical research and the development of new drugs. PGx can be used to select participants based on their genetic predispositions to respond to certain types of therapies, resulting in smaller, efficient, safer and more rapid clinical studies. For example, investigators can use information from preclinical studies that identifies genes linked to drug metabolism to genotype subjects recruited for phase I trials, enabling screening out subjects who are more likely to experience ADRs. Identification of polymorphisms in the drug target gene during phase I and phase II trials and their link to adverse effects or variation in drug response can be used to refine inclusion criteria in phase III clinical trials. Use of PGx in clinical trial design could yield as much as a three-fold reduction in clinical drug development time, from 10-12 years to as little as 3-5 years. This should increase the efficiency and lower the costs of new drug development.[125]

Adaptive clinical trials are emerging as a new approach to clinical trial design. This approach is grounded in the concept of selecting participants based on their expected response to certain types of therapies. The ability to identify critical biomarkers during the drug development process has allowed investigators to predict more accurately which patients will better respond to a given treatment. In an adaptive clinical trial, patient outcomes from early phases of the trial can be used to adjust the trial's allotment of future patients in subsequent stages,

[123] Pharmacogenetics Research Network. Bethesda, MD: National Institute of General Medical Sciences. Accessed March 5, 2007. http://www.nigms.nih.gov/Initiatives/PGRN/.

[124] Personalized medicine: the emerging pharmacogenomics revolution, 2005.

[125] Personalized medicine: the emerging pharmacogenomics revolution, 2005.

narrowing the sample selection to include only patients with a higher probability of having a positive outcome. Rather than selecting from a cross-section of the general population, adaptive trials can also be designed to favor random allocation from patient populations with characteristics (such as specific tumor markers in cancer patients) that are likely to predict positive outcomes.[126,127] Data can also be used to adapt treatment allocation, drop or add treatment arms, and allow seamless integration of phase II and III data sets.[128]

Clinical trial sponsors hope adaptive trial designs will better identify levels of drug safety and effectiveness faster and with smaller sample sizes, while simultaneously decreasing patient exposure to less effective treatments. As opposed to non-adaptive clinical trials in which all patient selection and related study design aspects are determined in advance, adaptive clinical trial designs are iterative, flexible, and able to fine tune themselves throughout the drug development process, potentially leading to more efficient and precise identification of effective treatments. Other benefits cited include observing positive treatment responses at an earlier stage in diseases such as cancer, as well as avoiding ethical dilemmas in conditions or diseases where clinicians and patients would balk at traditional randomization.[129]

The re-authorization of the Prescription Drug User Fee Act (PDUFA) signifies steps toward developing the necessary infrastructure for the uptake of adaptive trial designs. Under PDUFA IV, FDA will be developing a guidance on testing, detecting and preventing safety problems through enriched trial designs during drug development.[130,131] FDA representatives have also noted that adaptive clinical trials can play a role in the agency's Critical Path Initiative. This initiative includes the formation of the Predictive Safety Testing Consortium involving Critical Path and major pharmaceutical companies, where firms committed to share data on preclinical and clinical biomarkers to predict the safety of new treatments prior to human testing.[132]

While the use of adaptive trial design has clear benefits, experts in industry and academia have been quick to note potential pitfalls. Controversy remains over the use of adaptive design in later trials, particularly in phase III, because they have less statistical efficiency and the results are difficult to interpret. Adaptive trial design can be logistically complicated and complex to run, requiring a robust and integrated data system to manage information on drugs and trial participants. Some are concerned that these trials could result in unintentional unblinding and bias because they can preferentially select trial participants.[133]

Regardless of how clinical trials are conducted, for tests subject to FDA review, sponsors need to be sure that their studies are designed properly so that FDA's quality-of-evidence standards

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126 Kuehn BM. Industry, FDA warm to "adaptive" trials. JAMA 2006;296(16):1955-7.

127 Gottlieb S. Speech before 2006 conference on adaptive trial design, Washington DC. Rockville, MD: US Food and Drug Administration, 2006. Accessed February 27, 2007. http://www.fda.gov/oc/speeches/2006/trialdesign0710.html.

128 Critical Path Initiative: what it means for pharmaceutical industry statisticians. FDA/Industry Workshop September 14-16, 2005. Alexandria, VA: American Statistical Association, 2005. Accessed February 28, 2007. http://www.amstat.org/meetings/fdaworkshop/presentations/2005/G1_Offen_Critical%20Path.ppt

129 Gottlieb S 2006.

130 The future of drug safety – promoting and protecting the health of the public: FDA's response to the Institute of Medicine's 2006 report. US Food and Drug Administration, January 2007. Accessed February 6, 2007. http://www.fda.gov/oc/reports/iom013007.pdf.

131 Prescription Drug Use Fee Act. Federal Register 2007;72(9):1743-53.

132 FDA and the Critical Path Institute announce Predictive Safety Testing Consortium. Rockville, MD: US Food and Drugs Administration, 2006. Accessed February 28, 2007. http://www.fda.gov/bbs/topics/news/2006/NEW01337.html.

133 Kuehn BM 2006.

can be met. Recognizing the need to encourage and assist sponsors of PGx research, FDA has issued guidances for submission of PGx data during the drug development process and made recommendations to sponsors seeking FDA approval for PGx tests.[134,135] FDA evidence standards and PGx-related guidances are discussed in greater detail in Section III, *Gatekeepers.*

Recommendation 3

NIH should encourage sponsors and researchers to consult with FDA early in the study design phase so that study results can be used to support a pre-market review application. For example, studies should have sufficient statistical power, and quality controls should be in place.

NIH should also consider making FDA's quality-of-evidence standards a component of their assessments of the scientific merits of grant submissions.

D. Development of PGx Products

The following section provides an overview of the development of new drugs and diagnostic tests, co-development of drugs and diagnostics, and the application of PGx to existing drugs and to drugs that were found ineffective during drug development or withdrawn from the market.

1) Drug Development

Traditional drug development relies on the random assignment of sufficient numbers of enrollees with particular condition to investigational drug and control groups to enable detection of statistically significant drug responses. Some patients with a given condition may be less genetically predisposed to respond to the investigational medication than others. As such, it is typical to enroll large numbers of patients to ensure having enough to detect with statistical certainty any true treatment effect among those who are responsive to the medication. Any reported treatment effect is diluted across the full sample of enrolled patients. In contrast, the application of PGx to clinical trials can enable targeted selection of subjects and smaller trials by identifying those subjects more likely to respond to a drug based on their genotype.[136,137] PGx may lead to more precise and effective inclusion and exclusion criteria in clinical trials and can be used at multiple points in the drug development process.[138,139]

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134 Draft guidance for industry and FDA staff: commercially distributed analyte specific reagents (ASRs): frequently asked questions. Rockville, MD: US Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety, 2006. Accessed September 8, 2006. http://www.fda.gov/cdrh/oivd/guidance/1590.pdf.

134 Draft guidance for industry, clinical laboratories, and FDA staff: in vitro diagnostic multivariate index assays. Rockville, MD: US Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety, 2006. Accessed September 8, 2006. http://www.fda.gov/cdrh/oivd/guidance/1610.pdf.

136 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

137 Sadee W. Pharmacogenomics: the implementation phase. AAPS PharmSci 2002;4(2):1-6.

138 Emilien G, Ponchon M, Caldas C, et al. Impact of genomics on drug discovery and clinical medicine. O J Med 2000;93:391-423.

139 Issa AM 2002.

The application of PGx will be most clinically valuable when genotypes for adverse response and optimal efficacy for a given compound occur at a high frequency in the patient population.[140] By applying PGx-based stratification based on these genotypes, specific subgroups of subjects examined in phase III clinical trials would be expected to demonstrate greater response to and/or fewer adverse effects from the drug being studied.[141] These phase III trials likely would result in decreased drug development time and costs and potentially faster drug approvals.[142] It will continue to be difficult to detect rare adverse events in smaller clinical trials.[143]

The influence of PGx on drug development is difficult to predict. For example, concerns about potentially narrower markets, intellectual property matters, and uncertain regulation and reimbursement may add to the risk of undertaking development of PGx products.[144,145] On the other hand, PGx may allow for more products to reach market that otherwise would not have and may pose lesser risk of liability or market withdrawal due to fewer ADRs.

2) Diagnostic Test Development

While both involve testing of an individual's genome or gene products, there are differences between the broader concept of genetic testing and the more specific concept of PGx testing. Genetic testing originated, and continues to be used primarily, to determine the risk of developing a genetic-based condition or disease. PGx testing is a particular form of genetic testing that is used to inform therapeutic decisions, including whether to use particular drugs and in what doses. Most genetic testing, including PGx testing, is performed as an in-house service by clinical laboratories, although some can be performed using test kits.

As with any other type of diagnostic test, PGx tests vary in their sensitivity, specificity and predictive power. The clinical validity of these tests depends on these parameters.[146] Studies of tests for SNPs require population sample sizes that are large and diverse enough to assess associations in different sub-strata of the population.[147,148] In particular, sample sizes to validate a PGx diagnostic test should be sufficiently large to measure and compare drug responses between different genotype groups.[149,150]

A key concern related to the development of PGx diagnostic tests is projecting the utilization of the test and accompanying return on investment of test development, as well as the added costs

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140 Shah J. Criteria influencing the clinical uptake of pharmacogenomic strategies. BMJ 2004;328:1482-6.
141 Ibid.
142 Phillips KA, Veenstra DL, Ramsey SD, et al. Genetic testing and pharmacogenomics: issues for determining the impact to healthcare delivery and costs. Am J Manag Care 2004;10(7):425-32.
143 Shah J. Criteria influencing the clinical uptake of pharmacogenomic strategies. BMJ 2004;328:1482-6.
144 Bartfai T 2004.
145 New drug development: science, business, regulatory, and intellectual property issues cited as hampering drug development efforts. Report to Congressional requesters 2006. GAO-07-49. Washington, DC: United States Government Accountability Office. Accessed February 26, 2007. http://www.gao.gov/new.items/d0749.pdf.
146 Robertson JA, Baruch B, Buchanan A, et al. Pharmacogenetic challenges for the heath care system. Health Aff 2002;21(4):155-67.
147 Personalised medicines: hopes and realities, 2005.
148 Kirchheiner J, Fuhr U, Brockmöller J, Pharmacogenetics-based therapeutic recommendations – ready for clinical practice? Nature 2005;4:639-47.
149 Katz DA. From bench to bedside: a diagnosis framework for pharmacogenetics research. Mol Genet Metab 2002;77:57-60.
150 Kirchheiner J 2005.

of developing these tests. This is, of course, linked to the anticipated use of the therapies whose prescriptions will be informed by the PGx test. Individualized drug therapies may be cost-effective only for certain combinations of disease, drug, gene, and test characteristics, which should be evaluated accordingly.[151] Clinicians and payers will seek to use risk factors and other patient information to focus the use of such tests on those patients for whom the test results are likely to have clinical impact, particularly for tests that are expensive or that may lead to the use of expensive therapies.[152] Demand may be appreciable for tests that are developed to inform therapeutic decisions for prevalent chronic diseases, as more patient years of unnecessary or ineffective treatment can be avoided if patients are tested and treated appropriately.[153]

As is the case for new drugs, matters of intellectual property protection pertain to the development of PGx tests. There is uncertainty about what can be considered legally patentable material or method. Most PGx tests are based on the identification of a small number of SNPs that relate to various patient responses to medication. It is unclear whether actual gene variants can be patented as products.[154] Most patent claims likely will focus on methods of testing, methods of treatment arising from testing, and novel dosage forms. Intellectual property rights also will be at issue in the process of developing a test. For example, if the development of a PGx test requires access to DNA sequences protected by existing patents, a developing company may need to obtain licenses third parties, adding to R&D costs.[155] The issue of who will be granted patent rights is particularly complex given that multiple entities can be involved in the development of a diagnostic test.[156]

3) Co-development of Drugs and Diagnostic Tests

In PGx, co-development refers to the contemporaneous, linked development of drugs and tests.[157] Co-development occurs when drug makers investigate various biomarker strategies during the early stages of development, resulting in a validated biomarker that is identifiable with a diagnostic test. This makes it possible for FDA to review drug and diagnostic products simultaneously, potentially accelerating FDA approval process. However, there has been some resistance in the pharmaceutical industry to taking on such co-development.[158] One reason for this resistance has been concern in the industry that the market for the drug may be segmented into parts too small to be profitable. There has also been uncertainty regarding how FDA would regulate diagnostics and drugs developed by different manufacturers, considering that these products traditionally have been administered separately for regulatory, reimbursement, and clinical practice purposes. Furthermore, ambiguity remains about FDA regulatory review of "in-house" or laboratory-developed diagnostic tests, which traditionally do not traditionally require the same level of external data-review as tests sold to clinical laboratories. FDA's 2006 draft guidance on *in vitro* diagnostic multivariate index assays (IVDMIAs), however, may be a

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151 Veenstra DL, Higashi, MK. Assessing the cost-effectiveness of pharmacogenomics. AAPS Pharmsci 2000;2(3):article 29.

152 Flowers CR, Veenstra D. The role of cost-effectiveness analysis in the era of pharmacogenomics. Pharmacoeconomics 2004;22(8):481-93.

153 Veenstra DL 2000.

154 Barton JH. Patents, genomics, research, and diagnostics. Acad Med 2002;77(12):1339-47.

155 Pharmacogenetics: ethical issues, 2003.

156 Pharmacogenetics: ethical issues, 2003.

157 Drug-diagnostic co-development concept paper (draft). Rockville, MD: US Food and Drug Administration, 2005. Accessed May 2, 2006. http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf.

158 Wechsler J. Drug development linked more closely to diagnostics: manufacturers may need to produce diagnostic tests to gain FDA approval of new pharmacogenomic-based drugs and biologics. Pharmaceutical Technology; Oct 2004.

move toward reversing this policy, by extending FDA oversight over one type of in-house laboratory test.[159] This FDA draft guidance is discussed in more detail in Section III, *Gatekeepers.*

The drug development and validation process has traditionally involved separate development of drugs and diagnostic tests by individual manufacturers, without coordination of effort, such that the two products may not be available for use at the same time. The implications of this non-coordinated process are highlighted by the example of the development of the breast cancer drug, Herceptin. (See Exhibit 1.)

Exhibit 1. The Case of Herceptin

Herceptin, marketed by Genentech, is a monoclonal antibody indicated for about a quarter of breast cancer patients who have a genetic abnormality that leads to over-expression of the HER-2 protein. During product development, Genentech and FDA recognized that appropriate treatment required a diagnostic test to identify HER-2-positive individuals. Therefore, Genentech devised an assay for selecting patients for clinical trials. However, to grant market approval for the drug, FDA wanted the company to provide a HER-2 diagnostic test suitable for commercial use. Genentech initially collaborated with DAKO Corporation to provide such a test. The two manufacturers simultaneously filed applications for coordinated use of the drug and an immunohistochemistry (IHC) test, which measures the level of expression of the HER-2 protein in tumors, and gained FDA approval in late 1998. After Herceptin was on the market, though, Genentech found that the medical community remained uncertain about when it was appropriate to test patients for HER-2. Further research found that a test method based on fluorescence *in situ* hybridization (FISH), which detects the underlying gene alteration in the tumor cells by measuring the number of HER-2/neu gene copies,[160] and could better select those patients who could clearly benefit from Herceptin.[161] Genentech worked with the diagnostic firm Vysis to gain FDA approval of a FISH test and applied to FDA to change the label for Herceptin to include FISH testing as an alternative.[162] Even so, analyses of randomized trials of adjuvant therapy using Herceptin have shown that algorithms for testing for HER-2 had not been standardized and were developed arbitrarily.[163]

The development and marketing of Herceptin would not have been possible without specific diagnostic tests commercially available to identify HER-2-positive patients. Herceptin might have been approved earlier had there been a coordinated co-development effort for Herceptin and a diagnostic test to identify HER-2-positive patients.

Parallel development of drugs and diagnostics is a relatively new aspect of drug development and calls for careful coordination. As highlighted by the case of Herceptin, it can result in expedited drug approvals. In the sequential development approach, any scientific or technologic issues for one product may have substantial implications for the other. Clinicians may be more confident in the use of a diagnostic test if it is developed in conjunction with clinical trials for the indicated drug. Parallel development may diminish the need for post-approval label changes,

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159 Evans BJ. Distinguishing product and practice regulation in personalized medicine. Clin Pharmacol Ther 2007;81(2):288-93.

160 In tumor cells that are HER-2-positive, there are two or more copies (i.e., gene amplication) of the HER-2/neu gene per chromosome 17.

161 Ross JS, Fletcher JA, Bloom KJ, et al. HER-2/neu testing in breast cancer. Am J Clin Pathol 2003;120(Suppl):S53-71.

162 Herceptin product insert. South San Francisco, CA: Genentech, 2005. Accessed May 5, 2006. http://www.gene.com/gene/products/information/pdf/herceptin-prescribing.pdf.

163 Guideline summary: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor HER2 testing in breast cancer. J Oncol Pract 2007;3(1):48-50.

potentially reducing administrative burden on FDA and unnecessary confusion in clinical practice.[164] New product co-development in this field is being encouraged by FDA through its release of guidelines and concept papers clarifying some of the regulatory issues involved in the development of drugs and diagnostic tests.[165,166,167]

Recommendation 4A

FDA should build on its prior efforts to address the co-development of PGx drugs and diagnostics by developing a guidance document on this topic. FDA's guidance should clarify the review process for co-developed PGx products where the drug is subject to FDA review but the laboratory-developed companion diagnostic test may not be. It also should promote collaboration between drug and diagnostics manufacturers.

4) Using PGx to "Rescue" Drugs

PGx may provide an avenue for "rescuing" or reintroducing drugs that were found ineffective during drug development or were withdrawn from the market due to serious ADRs.[168,169] For instance, stratification of clinical trial subjects into subgroups can enable further development of drugs that would have otherwise failed due to the inability to detect significant treatment effects across larger groups of heterogeneous responders.[170,171,172] Just as with new drug development, genetic information can be used to target the study of these drugs to smaller populations.[173] In drugs for which trial outcome information is available by genotype, post-hoc analysis could identify subpopulations of high responders from among larger trial populations of low average response. Currently, DNA samples from clinical trial participants are collected for this type of PGx research in many early-stage clinical trials.[174,175]

PGx also could be used to reintroduce and remarket drugs that had been withdrawn from the market due to ADRs. PGx-generated data might demonstrate that an ADR is linked to a genetic variation that is identifiable through testing. Using this information, patients who would be at risk of experiencing an ADR could be identified before the drug is prescribed.[176] An example of a drug that FDA has begun to re-examine is Lotronex, a medication developed by GlaxoSmithKline to treat irritable bowel syndrome. Soon after receiving FDA approval, it was

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164 Drug-diagnostic co-development concept paper (draft), 2005.
165 Guidance for industry: pharmacogenomic data submissions, 2005.
166 Drug-diagnostic co-development concept paper (draft), 2005.
167 Draft guidance for industry and FDA staff: pharmacogenetic tests and genetic tests for heritable markers. Rockville, MD: US Food and Drug Administration, 2006. Accessed April 25, 2006. http://www.fda.gov/cdrh/oivd/guidance/1549.pdf.
168 Shah J. Economic and regulatory considerations in pharmacogenomics for drug licensing and healthcare. Nat Biotechnol 2003;21(7):747-53.
169 Pharmacogenetics: ethical issues, 2003.
170 Pharmacogenetics: ethical issues, 2003.
171 Personalized medicine: the emerging pharmacogenomics revolution, 2005.
172 Robertson JA 2002.
173 Phillips KA 2004.
174 Personalised medicines: hopes and realities, 2005.
175 Parent A, Noiseux M and Côté G. Potential for pharmacogenomics science and technology in Canada: pharmaceutical mirage or oasis? Montreal, Quebec: Science-Metrix, Canadian Biotechnology Secretariat, 2004. Accessed April 25, 2006. http://www.sciencemetrix.com/pdf/SM_2003_015_IC_Pharmacogenomics_Potential_Canada.pdf.
176 Pharmacogenetics: ethical issues, 2003.

withdrawn from the market after some patients experienced ADRs, including serious intestinal complications.[177,178]

Despite the potential application of PGx to rescue lost drugs, some have speculated that reintroduction of these drugs is unlikely to occur until PGx can be shown to result in clinically important improvements in the risk/benefit ratio for drugs with genetically-determined ADRs.[179] Drug developers are unlikely to pursue this avenue in instances where the patent for a drug has expired or for which an alternative treatment requiring no PGx testing exists.[180] Drug developers may be motivated to use PGx to develop new but similar drugs or to rescue drugs in cases in which there are no alternative treatments already available.[181,182]

5) *Application of PGx to Existing Drugs*

PGx has the potential to improve the safety and efficacy of existing drugs through the use of diagnostic tests that are predictive of drug response and avoid ADRs. As noted above, warfarin, an anticoagulant taken by more than a million people in the US, requires accurate dosing to avoid serious complications such as hemorrhaging. However, current dosing decisions for the drug are based primarily on clinical judgment. Warfarin is metabolized by the enzyme CYP2C9, certain variants of which are associated with an increased risk of bleeding.[183,184] Recent studies suggest that polymorphisms in the gene VKORC1 may explain some of the interpatient variation in response to warfarin treatment.[185,186,187,188] Development of a PGx test for these variants has been suggested as a means to identify those who may be at a higher risk of warfarin-associated bleeding.[189,190] Diagnostic manufacturers have a stake in PGx research for existing drugs to the extent that they can develop and own clinically useful tests based on genetic variants identified as a result of PGx research.[191]

The application of PGx to existing drugs, however, may not always add value. Where ADRs associated with a drug are considered minor and alternative drug treatments exist, it may be more practical and convenient to provide the drug and observe the patient's response than to use a PGx test to rule out the drug. If the drug does result in an ADR, then the patient can be

177 Pharmacogenetics: ethical issues, 2003.
178 Shah J 2003.
179 Shah RR. Can pharmacogenomics help rescue drugs withdrawn from the market? Pharmacogenomics 2006;7(6):889-908.
180 Shah J 2003.
181 Shah J 2003.
182 Pharmacogenetics: ethical issues, 2003.
183 Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 2005;7(2):97-104.
184 Humphries SE, Hingorani A. Pharmacogenetics: progress, pitfalls and clinical potential for coronary heart disease. Vascul Pharmacol 2006;44(2):119-25.
185 Sconce EA, Khan TI, Wynne HA, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood 2005;106(7):2329-33.
186 Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation of warfarin dose. New Engl J Med 2005;352(22):2285-93.
187 Li T, Lange L, Li X, et al. Polymorphisms in the VKORC2 gene are strongly associated with warfarin dosage requirements in patients receiving anticoagulation. J Med Genet 2006;[Epub ahead of print].
188 Monday, November 14, 2005 meeting of the Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science. Rockville, MD: US Food and Drug Administration, 2005. Accessed June 6, 2006. http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4194T1.pdf.
189 Pharmacogenetics: ethical issues, 2003.
190 Personalised medicines: hopes and realities, 2005.
191 Pharmacogenetics: ethical issues, 2003.

prescribed the alternative.[192] While ADRs can be reduced with PGx testing, PGx testing will not always offer clinical value. A recent study that analyzed 43 SNPs that had previously been implicated in response to the statin class of lipid management drugs found that only two SNPs had even a minor (about 3% additional) effect on the ability of just one of the statins to decrease low-density lipoprotein cholesterol (LDL-C), smaller than the known effects of the demographic variables of age and sex.[193]

The availability of funding for PGx research on existing drugs is likely to depend on the drugs' patent status. Drug companies may have a financial incentive to pursue further work on one of its drugs to extend its patent life. For example, PGx could lead to the identification of subpopulations with new indications for which an existing drug may be beneficial.[194] PGx can be used to identify new indications for existing drugs, extending their market life and profitability. Adding indications for existing drugs is less costly and time-consuming than developing new drugs.[195] Companies can readily obtain new patents for existing products by making small changes that do not introduce significant therapeutic benefits, including "product line extensions," such as changing drug dosage or tablet into capsule form. They also can develop new indications for already approved drugs whose patents have expired, and gain three more years of market exclusivity, i.e., during which identical generic products cannot be approved by FDA. Even so, this exclusivity would have little practical impact unless it involved a new dosing formulation or strength, especially if physicians could prescribe old forms of the drug for the new uses. As such, there is likely to be little financial incentive for a drug company to expand indications of a drug that is no longer under patent.[196]

6) PGx and Small Target Populations

PGx-based drugs are well-positioned to benefit from The Orphan Drug Act of 1983. The purpose of this law is to encourage the development of drugs for patient populations that are likely to be too small to generate sales large enough for drug makers to recoup their investment. Drug development is encouraged through multiple incentives, including seven years of exclusive marketing rights for drug manufacturers, tax credits for the cost of clinical research, grants to support research on new treatments for rare diseases, the elimination of user fees and, oftentimes, receiving expedited review for market approval. This law has been very successful, leading to FDA approval of more than 200 new orphan drugs, with hundreds more in the R&D pipeline. The provisions of The Orphan Drug Act are largely favorable for PGx-based drugs, as they can have a potentially large clinical impact on a small target population, may be intended for patients without effective treatment and may be validated by clinical trials involving smaller numbers of subjects than typically are enrolled.[197,198]

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192 Pharmacogenetics: ethical issues, 2003.

193 Thompson JF, Man M, Johnson KJ, et al. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. Pharmacogenomics J 2005;5352-8.

194 Issa AM. Pharmacogenomic profiling in post-marketing surveillance: prospects and challenges. Pharmacogenomics 2003;4(5):647-55.

195 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

196 New drug development: science, business, regulatory, and intellectual property issues cited as hampering drug development efforts. Report to Congressional requesters 2006. GAO-07-49. Washington, DC: United States Government Accountability Office. Accessed February 26, 2007. http://www.gao.gov/new.items/d0749.pdf.

197 Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. Pharmacogenomics J 2002;2(1):20-4.

Companies may seek to limit the size of the target populations for their products via narrowly defined indications, or project use of their products as second- or third-line treatments, in an effort to meet the population size criterion for orphan drugs. To the extent that PGx can lower clinical trial costs by targeting investigational therapies in smaller, shorter clinical trials, it may lower the cost hurdle of conducting clinical trials; this could increase the attractiveness of taking a targeted-population route to gain market entry for drugs that would not otherwise have been considered to be orphan products. Such developments could circumvent the intent of the Act and prompt greater FDA scrutiny of orphan drug applications.[199,200,201]

It is not clear whether FDA would recognize a PGx-based drug as an orphan product if it confers a large benefit to an orphan-sized population, yet confers a modest benefit to a much larger population. Also, prevalence criteria for orphan device status requires a much smaller threshold of 4,000 or fewer individuals compared to the 200,000 threshold for orphan drug status. Consequently, for some smaller genomically-defined subpopulations, the regulatory landscape could favor the development of PGx drugs but not their accompanying PGx diagnostics, which are generally regulated as devices by FDA. Co-development of PGx drugs and tests is generally desirable, since the PGx test results determine whether the drug is suitable for an individual. Policy options such as expanding the criteria for the Orphan Drug Act to include PGx tests, or raising the population threshold for an orphan device, have been suggested to assure available treatment options for all genomic-based populations.[202,203,204]

Recommendation 4B

HHS should identify and provide incentives to the private sector to encourage the development of PGx products for smaller markets. Options to consider might include financial incentives, expedited FDA review, and greater intellectual property protection.

E. Translational Research: From Development to Clinical and Public Health Practice

The scientific complexity of PGx affects the prospects for innovation, adoption and diffusion of PGx-based health care. Despite the large and growing body of information on the genetic basis for variable responses to drugs, most of this scientific knowledge has yet to be translated into clinical and public health practice. Converting PGx science into useful tests will entail establishing and conveying matters of analytic validity, clinical validity, clinical utility and accompanying ethical, legal and social implications of the test.[205]

To date, cancer, and breast cancer in particular, has been the main therapeutic area in which PGx has being used for diagnostic purposes. In breast cancer, immunohistochemistry (IHC)

198 Shah J 2003.

199 Ibid.

200 Loughnot D. Potential interactions of the Orphan Drug Act and pharmacogenomics: a flood of orphan drugs and abuses? Am J Law Med 2005;31(2-3):365-80.

201 Wood AJ. A proposal for radical changes in the drug-approval process. New Engl J Med 2006;355(6):618-23.

202 Melzer D 2003.

203 Collins FS, Green ED, Guttmacher AE, Guyer MS; US National Human Genome Research Institute. A vision for the future of genomics research. Nature 2003;422(6934):835-47. Epub 2003 Apr 14.

204 The Orphan Drug Act (as amended). Rockville, MD: US Food and Drug Administration, 2006. Accessed July 27, 2006. http://www.fda.gov/orphan/oda.htm.

205 Burke W, Atkins D, Gwinn M, et al. Genetic test evaluation: Information needs of clinicians, policy makers, and the public. American Journal of Epidemiology 2002;156(4):311-8.

and fluorescence *in situ* hybridization (FISH) are the most common assays used for determining HER-2/neu status in tumor tissue. However, there is comparatively little information about using these and other tests to monitor response to therapy and predict recurrence of breast cancer.[206,207]

Converting scientific discoveries to patient care poses a set of challenges. Discerning the links between genes and disease pathology for the purposes of informing drug discovery requires extensive biological, functional and pathway analysis. Also, associations among a disease or risk factor, a genetic marker, a test, a treatment and health outcomes can be confounded by co-morbidities, potentially adverse drug-drug interactions, and environmental factors. Other individual factors in play are age, sex, weight, additional genetic characteristics, health-related behaviors and compliance with treatment plans.[208] In addition, sensitivity, specificity, predictive values and other measures of accuracy need to be well-characterized and clinically defined in order to facilitate interpretation of test results. Moreover, the clinical utility of a PGx test depends on the timing and nature of its application, e.g., therapy selection, dosing, or therapy monitoring. Lastly, the information yielded must be linked to a clinical decision and action. Taken together, these intervening steps in the pathway from PGx-based test results to improved health outcomes can make it difficult for regulators, payers, clinicians, and patients to discern the utility of a PGx test.[209,210]

1) Clinical Validity and Clinical Utility

For the successful adoption of PGx into clinical and public health practice, a PGx test has to demonstrate analytic validity, clinical validity and clinical utility. *Analytic validity* is a measurement of how accurately and consistently the test assesses the presence of a specific genotype, while *clinical validity* refers to the accuracy with which a test predicts a given clinical outcome.[211,212] *Clinical utility* refers to the ability of a PGx test to inform clinical decision-making, prevent adverse health outcomes (e.g., morbidity, mortality), and predict outcomes considered important to individuals and families.[213] Assessing the actual clinical validity and utility of a test in practice should occur while researchers are measuring its analytic validity. If a test is analytically accurate, but would not be applicable or effective in practice, it may not be a cost-effective improvement in the delivery of care. Studies of the translation of PGx research and the use of PGx diagnostic tests in clinical practice indicate that health care providers perceive little evidence to date of the clinical validity and utility of PGx tests in clinical

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206 Bast RC, Ravdin P, Hayes DF, et al. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19(6):1865-78.

207 Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol 2005;23(3):619-29.

208 Personalised medicines: hopes and realities, 2005.

209 Coverage and reimbursement of genetic tests and services. Washington, DC: US Department of Health and Human Services, Secretary's Advisory Committee on Genetics, Health, and Society, February 2006.

210 Califf RM. Defining the balance of risk and benefit in the era of genomics and proteomics. Health Affairs 2004;23(1):77-87.

211 Human Genome Epidemiology. Rome, Italy: International Clearinghouse for Birth Defects Surveillance and Research/Centers for Disease Control. Accessed August 4, 2006. http://www.icbd.org/images/lectures/MKhoury-HumGenomeEpidemiol%20-cambridge_02_lecture1.PPT#396,23,Epidemiologic Approach to Genetic Tests.

212 Burke W, Atkins D, Gwinn M, et al. Genetic test evaluation: information needs of clinicians, policy makers, and the public. Am J Epidemiol 2002;156(4):311-8.

213 Grosse SD, Khoury MJ. What is the clinical utility of genetic testing? Genetics in Medicine 2006;8(7):448-450.

contexts.[214] Gathering such evidence is compounded by the fact that neither the CLIA program nor FDA (in the case of PGx tests developed as in-house laboratory tests) requires submission of such data for the test to be available for clinical use.

Different stakeholders may have different expectations for what constitutes a demonstration of clinical utility. For instance, while a 10% tumor response to chemotherapy can be a promising short-term outcome for certain cancers and may suffice for market clearance, it may be less compelling to clinicians and payers interested in knowing whether the chemotherapy affects survival.

Researchers have suggested criteria to assess the clinical validity and utility and, thus, the potential clinical impact of PGx tests.[215] For example, some studies indicate that a PGx diagnostic test should address an unmet medical need and lead to one or both of more effective drug therapy and/or a reduction in ADRs. As in other testing, higher sensitivity and specificity of PGx testing increases confidence in any clinical decisions made based on test results.[216] For example, tests with low sensitivity (which generates false negative results) can fail to identify patients who are at high risk for an ADR, or they can fail to identify patients who would benefit from a potentially effective treatment. If the ADR is serious or if the treatment is the only one that is effective for a disease with high mortality or morbidity, then a PGx test with low sensitivity poses great risk. PGx tests with low specificity (which generates false positive results) can incorrectly identify patients as being at high risk for an ADR, which may lead to lost opportunities to provide effective treatments to patients. Also, tests with low specificity can incorrectly identify patients as being likely responders to a treatment, which may lead to unnecessary use of an ineffective treatment and a lost opportunity to pursue alternative, potentially beneficial treatments.

For PGx to fulfill its potential, it must be incorporated into clinical and public health decision-making. However, the utility of a diagnostic test rests on the test's clinical validity as compared to existing technologies. PGx tests' predictive value will vary with the complexity of their targets, from simpler and highly predictive tests like those that identify variations of CYP450 enzymes to more complex tests that explore multigenic interactions and metabolic pathways.[217] At least twice as many drugs' effects are predicted by these complex, multigene factors than are predicted by a single gene.[218] Further, the predictive value of a test may not be static; as tests incorporate new knowledge about the etiology of a disease and the associated genetic loci, they may become more accurate.[219]

In addition to demonstrating the clinical validity of new technologies such as PGx tests, there is a growing need to demonstrate improved clinical outcomes that result from the use of these technologies in actual practice. The ultimate clinical outcomes of even highly accurate and

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214 Webster A, Martin P, Lewis G, Smart A. Integrating pharmacogenetics into society: in search of a model. Nat Rev Genet 2004;5:663-9.

215 Webster A, Martin P, Lewis G, Smart A. Integrating pharmacogenetics into society: in search of a model. Nat Rev Genet 2004;5:663-9.

216 Katz DA. From bench to bedside: a diagnosis framework for pharmacogenetics research. Mol Genet Metab 2002;77:57-60.

217 Personalised medicines: hopes and realities, 2005.

218 Melzer D 2003.

219 Yang Q, Khoury MJ, Botto L, Friedman JM, Flanders WD. Improving the prediction of complex diseases by testing for multiple disease-susceptibility genes. Am J Hum Genet 2003;72(3):636-49.

reliable PGx testing depend on how the test results affect clinician and patient treatment decisions, the effectiveness of the indicated treatment, potential drug interactions, patient compliance, and other intervening factors. Health care providers will need to integrate PGx test results with these multiple factors to guide treatment.[220,221] The complex information needs of clinicians pose a challenge on two fronts: first, understanding the interactions among factors contributing to clinical outcomes currently is limited due to the paucity of large-scale population studies that examine how complex combinations of genetic variants affect drug response; second, most health care providers do not currently possess the training to interpret the information available.[222,223] Available PGx information on drug labels appears to be inadequate for guiding treatment decisions; moreover, dosing recommendations based on PGx diagnostics are largely not yet available.[224]

There is also a growing desire on the part of payers and other health authorities involved in making resource allocation decisions for information on the cost-effectiveness of PGx products. Cost-effectiveness analysis is used to quantify the marginal (difference in) cost per marginal unit of effectiveness achieved with a test versus the standard of care. Although controversial, cost-effectiveness analyses can help guide decisions about how finite funds for improving health are best spent. To date, very little research has been conducted on the cost effectiveness of PGx interventions.[225] Pharmacoeconomic analyses regarding PGx that have been conducted to date are regarded as exploratory and inconclusive.[226, 227,228]

[220] Burke W, Atkins D, Gwinn M, et al. Genetic test evaluation: information needs of clinicians, policy makers, and the public. Am J Epidemiol 2002;156(4):311-8.
[221] Melzer D 2003.
[222] Personalised medicines: hopes and realities, 2005.
[223] Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.
[224] Phillips KA, Van Bebber SL 2005.
[225] Phillips KA, Van Bebber SL. A systematic review of cost-effectiveness analyses of pharmacogenomic interventions. Pharmacogenomics 2004;5(8):1139-49.
[226] Dervieux T, Bala MV. Overview of the pharmacoeconomics of pharmacogenetics. Pharmacogenomics 2006;7(8):1175-84.
[227] Phillips KA 2006.
[228] Phillips KA 2004.

Recommendations 5A – 5D

The adoption of PGx technologies will hinge on the availability of evidence of their analytic validity, clinical validity, clinical utility, and cost-effectiveness. The following steps should be taken to facilitate the establishment of the evidence base to support the integration of PGx technologies into clinical and public health practice.

5A. HHS should provide resources to identify and address evidentiary gaps in analytic validity, clinical validity, clinical utility, and cost-effectiveness of PGx.

To better inform evidence-based decision-making, HHS should facilitate the development of tools to improve the validity of findings from observational studies. These tools include high-quality data resources; improved methodologies in the design, conduct and analysis of observational studies; and empirical research on the levels of evidence and types of studies required for making decisions for various purposes (e.g., coverage, clinical guidelines, performance metrics) and different clinical contexts.

5B. HHS should initiate and facilitate collaborations between public (e.g., AHRQ, DVA, CDC, CMS, FDA, NIH) and private (e.g., private health insurance plans, pharmacy benefits managers, health care facilities with electronic medical records, clinical research databases or genetic repositories) entities to advance the generation and sharing of knowledge on the analytic validity, clinical validity, clinical utility, and cost-effectiveness of PGx.

5C. Drug and diagnostics manufacturers should conduct studies and disseminate results on the clinical utility of PGx (e.g., through publication in peer-reviewed journals), including statistically non-significant and negative findings. Alternately, manufacturers should make data publicly available to allow others to conduct and publish such studies.

FDA can promote such studies by encouraging manufacturers to submit the data as part of their pre-market applications and post-market surveillance. FDA can facilitate the dissemination of results by listing published studies on its website (e.g., via its Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels).

5D. NIH should provide mechanisms that promote interactions among basic, translational, clinical, and outcomes researchers for the identification of endpoints and data elements to be measured. The goal of these interactions would be to maximize the value and utility of basic and translational research data for downstream assessments of the clinical validity and clinical utility of PGx tests. NIH could facilitate such collaborations by adding field to the ClinicalTrials.gov database to identify clinical trials that could incorporate PGx study components.

2) Current Initiatives in Health Outcomes Research for PGx

In an effort to coordinate the evidence-based translation of genetic tests and genomic applications from research to clinical and public health practice, CDC's National Office of Public Health Genomics initiated the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) project in 2004. Through the work of the independent EGAPP Working Group, this project is integrating knowledge from existing US and international assessment processes to examine evidence on the readiness of tests for translation into clinical and public health practice. The first two EGAPP-supported evidence reports, conducted by AHRQ Evidence-based Practice Centers, were recently released by AHRQ. The EGAPP Working Group will soon release recommendations on the clinical use of these tests based on the findings of the two evidence reports. The Working Group also is currently reviewing PGx testing for the

gene UGT1A1, which produces an enzyme that affects metabolism of irinotecan, a drug for colorectal cancer.[229]

The evidence report published in November 2006 assessed the evidence that CYP450 polymorphism testing in adults entering selective serotonin reuptake inhibitor (SSRI) treatment for non-psychotic depression leads to improvement in outcomes, or if testing results are useful in medical, personal or public health decision-making. The investigators reported a lack of high-quality clinical studies examining CYP450 polymorphism testing in depression. There was mixed evidence regarding the association between CYP450 genotypes and SSRI metabolism, efficacy and tolerability in treatment of depression. The report found no evidence pertaining to whether testing leads to improvement in outcomes; whether testing results are useful in medical, personal or public health decision-making; or whether there are direct or indirect harms associated with testing or with subsequent management options. The investigators called attention to the need for good-quality data addressing these questions.[230]

In addition to EGAPP, CDC created the Human Genome Epidemiology Network (HuGENet), which assesses "the impact of human genome variation on population health and how genetic information can be used to improve health and prevent disease."[231] Its reviews highlight the current state of epidemiologic and clinical knowledge about particular human genetic variations, and describe gaps in current knowledge which may warrant additional research.[232] HuGENet reviews relevant to PGx include a meta-analysis of studies on the association between CYP450 and breast cancer, among others.[233]

Other agency efforts that will likely contribute to the evidence base for PGx include AHRQ's Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network and Centers for Education and Research Therapeutics (CERTs), a national demonstration program. The DEcIDE Network conducts accelerated practical studies focused on the outcomes, safety, comparative effectiveness, and appropriateness of health care products and services.[234] Similarly, the CERTs demonstration program focuses on advancing the use of therapeutics through research and education efforts.[235]

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[229] Evaluation of genomic applications in practice and prevention (EGAPP): implementation and evaluation of a model approach. Atlanta, GA: Centers for Disease Control and Prevention, Office of Genomics & Disease Prevention, 2007. Accessed February 28, 2006. http://www.cdc.gov/genomics/gtesting/egapp.htm.

[230] Testing for cytochrome P450 polymorphisms in adults with non-psychotic depression treated with selective serotonin reuptake inhibitors (SSRIs). Evidence Report/Technology Assessment #146. AHRQ Publication No. 07-E002. Rockville, MD: Agency for Healthcare Research and Quality, Duke University Evidence-based Practice Center, 2007. Accessed February 23, 2007. http://www.ahrq.gov/clinic/tp/cyp450tp.htm.

[231] Welcome to HuGENet. Atlanta, GA: Centers for Disease Control and Prevention, National Office of Public Health Genomics, 2006. Accessed December 4, 2006. http://www.cdc.gov/genomics/hugenet/default.htm.

[232] HuGE reviews. Atlanta, GA: Centers for Disease Control and Prevention, National Office of Public Health Genomics, 2006. Accessed December 4, 2006. http://www.cdc.gov/genomics/hugenet/reviews.htm.

[233] Ibid.

[234] DEcIDE Network & CERTs. Rockville, MD: Agency for Healthcare Research and Quality, 2007. Accessed March 4, 2007. http://effectivehealthcare.ahrq.gov/decide/index.cfm.

[235] Centers for Education and Research on Therapeutics: overview. AHRQ Publication No. 07-P000-EF. Rockville, MD: Agency for Healthcare Research and Quality, 2007. Accessed March 4, 2007. http://www.ahrq.gov/clinic/certsovr.htm

F. Infrastructure Enabling Research and Development

Integration of PGx into R&D will require an infrastructure to promote and support the sharing of PGx databases and repositories. To maximize their value, these databases and repositories will also need to be integrated and linked to clinical data sources.[236,237]

1) Data Sharing

Advances in PGx research have led to the creation of public and proprietary databases and data repositories for storing, retrieving and analyzing genetic and genomic data. These databases range from data sets collected by pharmaceutical companies during clinical trials to large population-based public genomic databases.[238,239] With some 65 biotechnology companies and a majority of large pharmaceutical companies worldwide currently are investing in PGx-related technologies, and more than 260 non-commercial research institutions also are exploring PGx, the number of data sets containing PGx data is thought to be large.[240] Use of PGx databases as research tools has the potential to lead to the identification of new drug targets, improved assessment of drug response and treatment leading to increased drug safety and efficacy, and reduced health care costs.[241,242,243]

Researchers have called for sharing of and open access to genotype data from PGx databases and repositories and corresponding drug-response phenotype data from clinical data sources.[244,245] Some observers call for reciprocity between researchers and pharmaceutical companies. For instance, investigators that draw on information from large public PGx databases are increasingly encouraged to return enriched data (e.g., data from clinical trials) to these databases.[246] Some researchers suggest that establishing and running open "personalized medicine" databases for archiving and analyzing group and individual patient data on associations between genotypes and drug-response phenotypes could lead to a significant return on investment in the form of reduced ADRs and improved pharmacotherapy.[247]

Several Federally-funded efforts are underway to facilitate data sharing. The NIH-funded PharmGKB is a shared, web-based central repository of PGx data from PGRN research and the research community at large.[248] In the short term, PharmGKB aims to serve as a resource to facilitate basic PGx research. In the long term, PharmGKB is expected to have an impact on the

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236 Goldman BR. Pharmacogenomics: privacy in the era of personalized medicine. NW J Tech Intell Prop 2005;4(1):83-99.
237 Gurwitz D, Lunshof JE, Altman RB. A call for the creation of personalized medicine databases. Nat Rev Drug Discov 2006;5:23-6.
238 Pharmacogenetics: ethical issues, 2003.
239 Vyas H, Summers R. An information-driven approach to pharmacogenomics. Pharmacogenomics 2005;6(5):473-80.
240 Hopkins MM, Ibarreta D, Gaisser S, et al. Putting pharmacogenetics into practice. Nat Biotechnol 2006;24(4):403-10.
241 Regnstrom K, Burgess DJ. Pharmacogenomics and its potential impact on drug and formulation development. Crit Rev Ther Drug Carrier Syst 2005;22(5):465-92.
242 Altman RB, Klein TE. Challenges for biomedical informatics and pharmacogenomics. Ann Rev Pharmacol Toxicol 2002;42:113-33.
243 Joly Y, Knoppers BM. Pharmacogenomic data sample collection and storage: ethical issues and policy approaches. Pharmacogenomics 2006;7(2):219-26.
244 Gurwitz D 2006.
245 Vyas H 2005.
246 Joly Y 2006.
247 Gurwitz D 2006.
248 Pharmacogenetics Research Network. Bethesda, MD: National Institutes of Health, National Institute of General Medical Science, 2006. Accessed May 4, 2006. http://www.nigms.nih.gov/Initiatives/PGRN.

delivery of care and will serve as a resource for researchers as well as health care providers, pharmacologists, policymakers, and the public. Toward meeting these goals, PharmGKB is supporting research projects in multiple areas. For example, the Pharmacogenetics Ontology Project aims to develop standardized mechanisms and taxonomies for organizing, annotating, and indexing PGx data to assist researchers in integrating information about how variation in genotype is linked to variation in phenotypic response to drugs.[249] Another federally-funded database, the dbSNP, which arose from a collaboration between NCBI and NHGRI, represents the largest public repository of SNP data in the world. These data are contributed from multiple sources, including individual laboratories, large-scale sequencing centers, and industry sources.[250] NCI's cancer Biomedical Informatics Grid (caBIG) is another data sharing effort that is an information network intended to link researchers, physicians and patients throughout the cancer community in order to collect and disseminate data on cancer research and care.[251]

Industry is unlikely to share what it considers proprietary data without some assurances that any patents and data they have specified as confidential are protected before restatement or publication. Additionally, companies may seek legal arrangements stipulating that they would share intellectual property or commercial product development and still retain the ability to pursue and market the product independently. Even with such agreements, industry may remain circumspect about sharing their data with others.

The Federal government has generally discouraged users of its public databases to seek patents on findings or products derived from the shared data. NIH's database of Genotype and Phenotype (dbGaP), which will archive and distribute findings from studies that investigate the interaction of genotype and phenotype, specifies that data submitted to dbGaP will be pre-competitive and will not be protected by intellectual property patents.[252] A new proposed NIH policy that creates a centralized GWAS data repository encourages patents for downstream discoveries, but discourages patenting of early information that could slow future research.[253,254]

Despite these seeming deterrents to data sharing, there is some indication that companies are becoming more aware of the potential benefits.[255] In February 2007, Novartis made the results of their genomic analysis of type 2 diabetes available at no cost on the Internet. The data resulted from a joint effort between Novartis and two academic institutions to identify genetic variants that influence risk of type 2 diabetes. The academic institutions agreed to work with Novartis provided that the data would be made publicly available; this also allowed them to collaborate without competing with each other on patent issues. Given that the large magnitude of data, Novartis views this as an opportunity to "lure in researchers who identify

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[249] PharmGKB: The Pharmacogenetics and Pharmacogenomics Knowledge Base. Palo Alto, CA: Stanford University, 2006. Accessed May 4, 2006. http://www.pharmgkb.org/index.jsp.

[250] Vyas H 2005.

[251] Cancer Biomedical Informatics Grid (caBIG). Bethesda, MD: National Institutes of Health, National Cancer Institute, 2007. Accessed February 23, 2007. http://cabig.cancer.gov/index.asp.

[252] About dbGaP. Bethesda, MD: National Institutes of Health, National Center for Biotechnology Information, 2007. Accessed March 4, 2007. http://www.ncbi.nlm.nih.gov/entrez/query/Gap/gap_tmpl/about.html.

[253] Genome-Wide Association Studies (GWAS). Bethesda, MD: National Institutes of Health, Office of Extramural Research. Accessed March 7, 2007. http://grants.nih.gov/grants/gwas/index.htm.

[254] Fact Sheet on genome-wide association studies (GWAS) proposed policy. Bethesda, MD: National Institutes of Health, Office of Extramural Research, 2006. Accessed March 7, 2007. http://grants.nih.gov/gwas/fact_sheet.htm.

[255] Pincock S. Pharma goes open access: Novartis shares diabetes genomic data, and experts say there's more to come. The Scientist 2007. Accessed March 1, 2007. http://www.the-scientist.com/news/home/52891/

leads from the data." If researchers find results to help treat or cure diabetes, Novartis hopes that they will want to return to Novartis to collaborate on the development of a corresponding drug.[256] Similarly, Pfizer and Affymetrix, along with Abbott Laboratories, have recently formed a public-private partnership with NIH called the Genetic Association Information Network (GAIN). This collaboration, which also will include other stakeholder partners (e.g., private foundations, advocacy groups), intends to provide open, equal access to data from whole genome association studies using samples from existing case-control studies of patients with common diseases.[257]

Recommendations 6A & 6B

6A. HHS should encourage private sector entities (including academic institutions) to voluntarily share proprietary data to advance the development and co-development of PGx products.

6B. HHS should work with the private sector to identify obstacles to data sharing and to develop solutions to overcome these obstacles (e.g., legal and data confidentiality assurances, intellectual property protections).

2) Linking Databases

Although important efforts are underway to promote data sharing, the integration of genomic and clinical information remains at an early stage.[258] Data collection, storage, modeling and transfer within and among PGx databases create challenges to infrastructure and support.[259] At present, the respective realms of genomic, molecular, cellular, clinical, and public health data exist with separate funding streams, stakeholder groups, administrative protocols and organizational cultures. Data format variation in disparate databases makes it difficult to achieve consistent integration and data exchange.[260] Advances in health IT promise to provide future connections between research databases and clinical records, though this data-intensive enterprise is years away from being fully adopted into day-to-day clinical practice and clinical information systems. Issues of data standardization, physician decision support, as well as confidentiality and privacy concerns also will need to be addressed before this can occur. Efforts by researchers to integrate PGx and clinical information likely will prompt ethical, legal and social concerns, such as patient consent and data protection, which may affect the willingness of patients, clinicians and health care managers to participate in PGx research and applications of this information in clinical practice. [261]

256 Ibid.

257 Genetic Association Information Network (GAIN). Bethesda, MD: Foundation for the National Institutes of Health, 2006. Accessed March 2, 2007. http/www.fninh.org/GAIN/Gain_home.shtml.

258 Hoffman MA. The genome-enabled electronic medical record. Journal of Biomedical Informatics 2006;[Epub ahead of print].

259 Altman RB 2002.

260 Vyas H 2005.

261 Joly Y 2006.

Recommendation 6C

Research, regulatory, medical record and claims databases need to be interoperable to facilitate research on PGx technologies and build the necessary evidence base. Interoperability of these databases will facilitate the study of the molecular pathogenesis of disease; the identification of targets for drug development; validation of PGx technologies; assessment of health outcomes associated with use of PGx technologies; and determination of the cost-effectiveness and economic impact of using these technologies.

HHS and other relevant Departments (e.g., DVA, DOD) should work with the private sector to improve data sharing and interoperability among databases. Specifically, HHS should work with existing organizations to create uniform genomic data standards; explore ways to harmonize data analysis methodologies; and develop an infrastructure to enable data exchange. Comparable efforts to standardize phenotypic data are also needed.

3) Collaborations

If data sharing and data linking are to advance research and enable further development and co-development of PGx products, collaborations among researchers, clinicians, industry and government are key. FDA's Critical Path Initiative aims to encourage public and private sector collaborations toward development of PGx products. The initiative sponsors the Opportunity List and Report that describes new scientific discoveries and how they can be used to improve test accuracy for evaluating the safety and efficacy of newly developed medical products.[262] Collaborations resulting from this initiative should help to promote sharing of research and clinical data and could lead to targeted areas of PGx research. As is the case for other aspects of implementing the Critical Path Initiative, additional funding from Congress may be required.[263]

Recommendation 6D

FDA should identify, initiate and facilitate research opportunities and public/private partnerships to encourage the development and co-development of PGx products, e.g., through the Critical Path Initiative.

G. Ethical, Legal and Social Issues in Research and Development

PGx research and development raises several ethical, legal, and social issues. This section discusses issues related to protection of personal information, informed consent, genetically-based identity, and liability.

1) Protection of Personal Information

PGx research involves management of DNA samples, demographic data and medical records. Participation in PGx research and experiencing PGx-based care in clinical practice may present risks for patients, including those posed by sharing genomic information. As genomic research expands towards undertaking population-based studies, the risks involved with the storage of large-scale sequencing information through databases will multiply. Maintaining the

[262] The Critical Path to new medical products. Rockville, MD: US Food and Drug Administration, 2006. Accessed July 27, 2006. http://www.fda.gov/oc/initiatives/criticalpath/.

[263] Pharmacogenetics: ethical issues, 2003. http://www.nuffieldbioethics.org/fileLibrary/pdf/pharmacogenetics_report.pdf.

confidentiality of these records is essential.[264,265,266] However, data protections must be weighed against constraints on data access and utility that would impede beneficial applications of data.

PGx research often involves human specimens (e.g., blood or tissue), particularly the use of coded specimens. The National Bioethics Advisory Commission defines unlinked or "anonymized" specimens as those that lack identifiers or codes and therefore cannot be linked to an individual. In contrast, coded specimens are specimens that receive a code when given to an investigator, but can still be traced to a particular individual using a code key.[267] Coded samples can be critical in PGx research, where genetic information from tissue samples may need to be correlated with clinical outcomes in order to understand how genetic variation affects drug response.

Continued efforts are needed to improve coding or encryption of data, particularly as more sophisticated means arise to overcome these protections. Existing technical approaches may not be sufficient to preserve privacy protection of genomic information, because an individual may be identified from very few SNPs.[268] Researchers have demonstrated that much information considered to be "de-identified" can be re-identified using readily available information. Limited-release strategies may be impractical to the extent that they constrain the use of data for patient care. Stronger privacy firewalls could impede data access and the ability to notify participants about research findings.[269,270]

Various technical, social and legal methods of protecting confidential information from misuse have been proposed or implemented. A 2006 NHGRI Workshop on Privacy, Confidentiality and Identifiability in Genomic Research outlined the need to strike a balance between "protecting and respecting" the privacy and confidentiality of patients and subjects while fostering efficient access to data for genomic research. Several approaches to protecting the identity of subjects were suggested, such as limiting the amount of genomic information released from each sample, statistically degrading or scrambling data before it is released and removing identifying data prior to coding the information. Also recommended was a shift towards controlled data-release arrangements, where parties must commit to protecting privacy and confidentiality before being granted access.[271] Some observers have suggested that the combination of a national biobank along with laws and policies for preventing misuse of data could help to reduce the risk of confidentiality breaches while enabling researchers' access to large volumes of data.[272] Still, public and policymaker skepticism regarding the security of a highly visible, centralized repository would need to be addressed. Others suggest the use of

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264 Personalized medicine: the emerging pharmacogenomics revolution, 2005.

265 Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.

266 Rothstein MA, Epps PG. Ethical and legal implications of pharmacogenomics. Nat Rev Genet 2001;2(3):228-31.

267 Research involving human biological materials: ethical issues and policy guidance. 1999 Vol. 1. Bethesda, MD: National Bioethics Advisory Commission. Accessed March 2, 2007. http://www.georgetown.edu/research/nrcbl/nbac/hbm_exec.pdf

268 Lin Z, Owen AB, Altman RB. Genetics. Genomic research and human subject privacy. Science 2004;305(5681):183.

269 Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.

270 Joly Y, Knoppers BM, Nguyen MT. Stored tissue samples: through the confidentiality maze. Pharmacogenomics J 2005;5(1):2-5.

271 Summary of the NHGRI workshop on privacy, confidentiality and identifiability in genomic research. Bethesda, MD. October 3-4, 2006. Bethesda, MD: National Human Genome Research Institute, 2006. Accessed February 23, 2007. http://www.genome.gov/19519198.

272 Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.

honest broker systems for the protection of privacy. These systems are intended to prevent the researcher from accessing identifiable research data and tracing this information back to patients.[273] Currently, the American Health Information Community (AHIC) is taking steps to ensure the protection of health data as part of a national health information infrastructure.

Recommendation 7

As data access and sharing expand, it will be important to strike the right balance between protecting the privacy and confidentiality of personal data and fostering access to these data for PGs research. Stronger data security measures may be needed as more PGx researchers access patient data.

2) Informed Consent

PGx may raise special concerns related to informed consent. For instance, PGx testing may be a condition of treatment, as set forth by clinical practice guidelines or payment policies (e.g., in the form of prior authorization or utilization review). Some consider this to be coercive, since consenting to a PGx test may be required to gain access to a treatment.[274] This issue can also arise when PGx testing is a condition of enrollment in a clinical trial of an investigational drug. Subjects may feel compelled to consent to genotyping in order to gain access to the study agent.

Informed consent also can be a challenge when coded specimens are being used. In recent years, informed consent requirements for the use of coded specimens have varied under two different regulations intended to protect individuals participating in clinical research. One set of regulations administered by the Office for Human Research Protections (OHRP), the HHS Protection of Human Subjects regulations and contained in Title 45 CFR Part 46, protects the rights and welfare of human subjects involved in research conducted or supported by HHS. A second set of regulations contained in Title 21 CFR Parts 50, 56, and 812 applies to clinical investigations over products regulated by FDA. The FDA and HHS human subject protection regulations differ in several significant ways.

Under the HHS regulations at 45 CFR Part 46, research using samples that are anonymized is not considered to be human subjects research within the definition of "human subject". Therefore, the requirements of 45 CFR Part 46, including the informed consent requirements, do not apply.

In addition, in 2004, OHRP issued guidance stating that research using coded human specimens would also not be considered human subjects research if: 1) the specimens were not collected specifically for the proposed research through interaction or intervention with living individuals; and 2) the investigator(s) cannot readily ascertain the identity of the living individuals to whom the specimens pertain because procedures are implemented that prohibit

[273] Gilbertson JR, et al. Automated clinical annotation of tissue bank specimens. MedInfo 2004:607-610. Pittsburgh, PA: Pennsylvania Cancer Alliance. Accessed March 8, 2007. http://pcabc.upmc.edu/publications/Medinfo2004_5711Gilbertson.pdf

[274] Personalised medicines: hopes and realities, 2005.

the release of the key to the code to the investigator(s) under any circumstances until the individuals are deceased.[275]

In contrast, the definition of a human subject under FDA regulation of *in vitro* diagnostic device studies is more stringent than the Common Rule and includes any individuals whose specimens could be traced to their identity. As such, informed consent is required before specimens can be used in FDA-regulated research and waivers are permitted only in research involving emergent or life-threatening situations. The discrepancies between these two policies has had ramifications for the translation of PGx discoveries into clinically useful treatments, since differing informed consent requirements have been applied at different points along the continuum between basic, upstream research and studies aimed at seeking approval of commercial products.[276]

Various groups have called for a more uniform approach to the regulation of human subjects research.[277] In 2006 guidance, FDA announced that increasing discretion would be used with these regulatory consent requirements, allowing the use of coded specimens if researchers elect to implement a set of voluntary privacy protections described in the guidance.[278] This policy brings FDA's regulatory approach more in line with that of OHRP, though it does not completely harmonize them.

HHS agencies are aware of the inconsistencies in federal policies governing clinical research. The NIH is currently dedicating resources to the harmonization of federal policies to address issues related to the protection of human research subjects. For example, the Clinical Research Policy Analysis and Coordination program (CRpac) was established in 2004 as part of the NIH Roadmap to promote the coordination of clinical research policies such as those involving human biological materials and data.[279] These activities reflect an ongoing effort to create an overarching ethical and legal framework for such research.

Achieving the appropriate level of informed consent for a given research or clinical scenario is an important consideration in PGx research; broad consent may lead to uninformed choice on the part of research subjects, while narrow consent can hinder research. Additional guidance may be needed to help investigators design consent processes that maximize benefits from research while preserving adequate levels of choice.

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[275] Guidance on research involving coded private information or biological specimens. Washington, DC: Office for Human Research Protections. Accessed March 2, 2007. http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm

[276] Evans BJ, Meslin EM. Encouraging translational research through harmonization of FDA and Common Rule informed consent requirements for research with banked specimens. J Leg Med 2006;27(2):119-66.

[277] Ethical and policy issues in research involving human participants. Bethesda, MD: National Bioethics Advisory Commission 2001. Accessed My 3, 2006. http://www.georgetown.edu/research/nrcbl/nbac/human/oversumm.html.

[278] Guidance on informed consent for *in* vitro diagnostic device studies using leftover human specimens that are not individually identifiable. Guidance for sponsors, institutional review boards, clinical investigators and FDA staff. April 25, 2006. Rockville, MD: The United States Food and Drug Administration. Accessed March 2, 2007. http://crpac.od.nih.gov/FinalFDAGuidanceonICforIVDDeviceStudieswithLeftoverSpecimensthatAreNotIndividuallyIdentifiable.pdf

[279] Clinical Research Policy Analysis & Coordination. Bethesda, MD: National Institutes of Health, 2006. Accessed June 6, 2006. http://crpac.od.nih.gov/about.asp

3) Population Stratification in PGx Research and Development

Most available diagnostics and drugs are developed based on clinical performance and outcomes data for groups in the general population with certain risk factors or indications. Trials often include diverse populations, which enable collecting data on drug response in the various groups who might later be prescribed the drug. Drug development and use in current clinical practice typically do not entail understanding of how inter-individual genomic variations alter drug response.

PGx's premise of individualizing drug treatment relies on stratifying these diverse populations into smaller subpopulations that may be predisposed to ADRs based on particular genomic profiles.[280] Although genetic characteristics may vary according to racial or ethnic origin (e.g., there is a high frequency the gene for the CYP2D6 enzyme among Ethiopian and Saudi Arabian populations that results in markedly increased metabolism of many medicines, whereas 7% of Caucasians have a genetic variants that results in reduced activity of this enzyme), these divisions between subpopulations often are determined using ethnic or racial or other demographic information as a proxy for more precise selection criteria. For example, FDA recently approved BiDil for the treatment of heart failure in self-identified black patients.[281,282] FDA approval of BiDil continues to generate controversy; some researchers have questioned the existence of disparities between African-American and other heart-failure patients and the motivations of BiDil's developers and manufacturer, recommending that physicians prescribe the drug as they see fit, regardless of a patient's race.[283] Still others continue to argue the merits of specifying the use of BiDil by African Americans.[284] Experience to date with the diffusion of BiDil and its reimbursement underline uncertainties and risks that may be associated with targeted therapies. (See Exhibit 2).

Exhibit 2. The Case of BiDil

A recent high-profile example of population stratification in research and development is FDA's approval of BiDil (hydralazine and isosorbide dinitrate) for the treatment of heart failure in self-identified black patients. This approval was based mainly on results of the African American Heart Failure Trial (A-HeFT) involving self-identified black enrollees.[285] Although skin color and other racial identifiers are not associated with most genetic variation in populations and rarely mediate drug response, conventional identifiers for race and ethnicity are sometimes used as proxies for genetic information. Drug labeling linked to racial characteristics is ambiguous and clinically sub-optimal, partly because there is no standard, objective means of identifying a "self-identified black" population. While the drug may benefit some patients who self-identify as black, it may not benefit others and could be effective for some non-black patients.[286] The availability of a genetically-based diagnostic to predict BiDil response is likely to be more sensitive and specific than designating treatment by conventional racial identifiers. This could widen access to a drug that would be effective for those who otherwise would have been

280 Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.

281 FDA approves heart drug for black patients. Rockville, MD: US Food and Drug Administration, FDA Consumer Magazine, 2005. Accessed May 1, 2006. http://www.fda.gov/fdac/features/2005/505_BiDil.html.

282 Kahn J. Genes, race and population: avoiding a collision of categories. Am J Public Health 2006;96(11):1965-70.

283 Sankar P, Kahn J. BiDil: race medicine or race marketing? Health Aff (Millwood) 2005;[Epub ahead of print].

284 Puckrein G. BiDil: from another vantage point. Health Aff 2006:w368–w374 (published online 15 August 2006; 10.1377/hlthaff 25.w368).

285 FDA approves heart drug for black patients. Rockville, MD: US Food and Drug Administration, FDA Consumer Magazine, 2005. Accessed May 1, 2006. http://www.fda.gov/fdac/features/2005/505_BiDil.html.

286 Sankar P, Kahn J. BiDil: race medicine or race marketing? Health Aff (Millwood) 2005;[Epub ahead of print].

excluded and could curtail use of the drug for those who would have been included but who would not have benefited.

Of particular note regarding the market potential of targeted therapies are recent reports indicating that prescriptions of BiDil are far below projections made at the time of its approval by FDA. According to a 2006 report in *The Wall Street Journal*, only about 1% of the 750,000 African-Americans with heart failure have prescriptions for BiDil. This unexpected development is reportedly due to health plan resistance to paying the premium price of this branded drug, estimated by the Department of Veterans Affairs to be between $1,382 and $2,765 annually per patient. Many health plans instead pay for the two inexpensive generic drugs that comprise BiDil, even though dosing the generic drugs in a manner that equates with their levels in BiDil poses challenges to patient compliance. The cost of BiDil presents a particular burden to low-income elderly patients at a time when drug coverage for many "dual eligibles" for Medicaid and Medicare has shifted from typically low monthly costs for most drugs under Medicaid to Medicare Part D plans that either do not cover BiDil or only offer it with expensive patient copayments. Since the approval of the drug in 2005, the stock price of its manufacturer, NitroMed Inc., dropped from $23 to under $3 a share by October 2006, according to the report.[287]

The use of concepts such as race and ethnicity in the context of health care is controversial.[288] Given the considerable genetic variation within conventional or self-identified racial and ethnic groups themselves, attempts to use population categories designated by race or ethnicity as proxies for genetic variation are likely to be scientifically suboptimal and medically impractical.[289,290] It can result in imprecise prescription guidelines and reinforce a public view of biologically-defined race.[291,292]

The implications for such stratification by race and ethnicity can have negative effects on uptake of PGx-related diagnosis and treatment. One possibility is a bias toward development of medicines in certain patient populations over other populations. This could be attributed to scientific expedience if it is easier to demonstrate statistically significant treatment effects in shorter clinical trials with smaller sample sizes of particular patient groups who are more likely to respond to an investigative therapy. Alternatively, it may be due to socioeconomic reasons, e.g., if a particular racial group in a wealthy country represents a potentially more lucrative market for a new therapy than patients of other racial backgrounds with the same condition in developing countries. These scenarios raise concerns about equity of drug development, including benefits and risks, for particular population groups.

The case of BiDil reflects recent uses of race and ethnicity as a basis for patenting drugs and securing market share. Recent reports have indicated that scientists conducted similar race-specific trials for the cancer drug Iressa and the statin Crestor.[293] A review of claims and abstracts of patent applications since 1976 reflects a five-fold increase in the use of racial

287 Westphal SP. Heart medication approved for blacks faces uphill battle. Wall Street Journal. October 16, 2006:A1.

288 Weber W. Pharmacogenetics. New York, NY: Oxford University Press, 1997.

289 Lee SS. Racializing drug design: implications of pharmacogenomics for health disparities. Am J Public Health 2005;95(12):2133-8.

290 Shanawani H, Dame L, Schwartz DA et al. Non-reporting and inconsistent reporting of race and ethnicity in articles that claim associations among genotype, outcome, and race or ethnicity. J Med Ethics 2006;32:724-8.

291 Pharmacogenetics: ethical issues, 2003.

292 Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.

293 Herper M. Race-based medicine arrives. Forbes 2005. New York, NY: Forbes Magazine. Accessed February 27, 2007. http://www.forbes.com/home/healthcare/2005/05/10/cx_mh_0509racemedicine.html.

categories in gene-related patents.[294] This type of intellectual property protection could lay the foundation for commercial ventures in which pharmaceutical companies market products to specific social groups based on the related prevalence of certain genetic variations. In the case of BiDil, NitroMed's race-specific patent grants them monopoly control over the market until 2020 for the use of the drug in African-American patients, while their patent over the use of BiDil in the general population expires in 2007.[295]

Though some industry observers believe that market segmentation will be financially advantageous, others view population stratification as having a negative economic impact on their market for drugs. One developer of an acne drug reportedly abandoned the product upon learning that FDA approved it with the requirement that prospective users be tested for an ADR-associated enzyme deficiency, thus decreasing the drug's market size.[296]

Stratification by race and ethnicity may also result in potential bias toward particular racial or ethnic groups if perceived or actual affiliation with that group is used as a proxy for a genetic profile. Aside from implications for equity, this may be scientifically unjustifiable, since not every member of the group could be expected to have the genetic variant in question. A study conducted by researchers at the National Cancer Institute (NCI) determined the prevalence of BRCA1 and BRCA2 mutations among Ashkenazi Jews in the Washington, DC, area. The researchers reported that 2% of this population carried a mutation in these genes, conferring a 56% risk of breast cancer and 16% risk of ovarian cancer by age 70. (Notably, the reported risk of breast cancer in this study for women with these mutations, 56%, was lower than previous estimates on the order of 85%).[297] While no individuals were identifiable as a result of this study, the population of Ashkenazi Jews—available as a local sample to the NCI research team—was identified as having particularly high risk of cancer relative to the general population. This could reinforce labeling of this group by employers and payers, as well as the public. However, this is misleading. Every person probably carries roughly the same number of genetic mutations that could lead to disease. Yet, more is known about the prevalence of mutations in certain population groups, including Finns, Icelanders, Ashkenazi Jews and Mormons, largely because researchers have found these groups more convenient to study. This arises for reasons such as their being identifiable as a genetically linked population, the availability of accurate genealogical records and, perhaps, a higher likelihood of being committed to public health or awareness of the potential medical and public health benefits.[298,299]

FDA has provided guidance on standardized collection of race and ethnicity information.[300] The guidelines assist researchers in collecting race and ethnicity data during clinical trials. In most cases, these data are self-reported, including a provision allowing individuals to designate

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294 Kahn J. Patenting race. Nat Biotechnol 2006;24(11):1349-51.

295 Ibid.

296 Pollack A. A special drug just for you, at the end of a long pipeline. The New York Times. November 8, 2005.

297 Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997;336:1401–8.

298 Lehrman S. Jewish leaders seek genetic guidelines. Nature 1997;389(6649):322.

299 Tryggvadottir L, Sigvaldason H, Olafsdottir GH, et al. Population-based study of changing breast cancer risk in Icelandic BRCA2 mutation carriers, 1920-2000. J Natl Cancer Inst 2006;98(2):116-22.

300 Guidance for industry: collection of race and ethnicity data in clinical trials. Rockville, MD: US Food and Drug Administration, 2005. Accessed July 27, 2006. http://www.fda.gov/cber/gdlns/racethclin.htm.

multiracial identity. While FDA collects race and ethnicity data for broad group statistical and reporting purposes, collection of such data at the individual and subgroup level may be less apt for scientific and medical research.[301] Gathering more specific genomic data in clinical trials, rather than traditional racial and ethnicity categorization, could lead to a more concrete understanding of the genetic bases of health issues.

Recommendations 8A & 8B

8A. Because genomic factors may be more meaningful predictors of drug response than race and ethnicity categories, FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may better explain differences in drug response.

8B. When drugs are shown to be effective in certain racial and ethnic subpopulations (e.g., BiDil), FDA should encourage manufacturers to conduct additional post-market studies to identify biological, social, behavioral and environmental markers that may underlie the differential drug response.

4) Liability Concerns for PGx Drug and Diagnostic Developers

Pharmaceutical companies are subject to liability for ADRs. These companies limit their liability by warning of known risks on drug labels. Requiring PGx testing as a condition for drug treatment could further reduce pharmaceutical companies' liability risk.

Developers of PGx-based diagnostics also face potential liability risks if PGx test results are incorrect or misinterpreted. Exposure to product liability for PGx testing may depend on whether a test is made available as a product, i.e., as an IVD, or in-house by a clinical laboratory. In the latter case, the clinical laboratory provides a service, i.e., the test results, rather than a product, and is therefore not subject to liability for product defects. As demand for more rapid turnaround of PGx test results increases, and if regulatory oversight of laboratory-developed tests by CLIA and FTC is strengthened, more tests are likely to be offered as kit products. These potential changes could expose companies that manufacture, distribute or interpret genetic tests to product defect liability.[302]

[301] Haga S, Venter C. FDA races in wrong direction. Science 2003;301(5632):466.
[302] Ossorio PN. Product liability for predictive genetic tests. Jurimetrics J 2001;41:239-60.

III. Gatekeepers

The process from early development of a PGx concept to successful use in practice is influenced by multiple agents. Some of these agents function as gatekeepers in that they can enable, halt, or redirect the course of a technology. The sections that follow describe four main gatekeepers relevant to the current and future use of PGx, including industry, FDA, CMS and other third-party payers, and developers of practice guidelines and other clinical standards.

A. Industry

Pharmaceutical, biotechnology and diagnostics manufacturers are important gatekeepers for PGx because their perceptions of risk and return on investment will influence whether and how they will pursue development, approval and marketing of new PGx products.

1) Use of PGx in Drug Development

One of the main concerns of industry and those with a stake in innovation is that the use of PGx to target products to particular population subgroups could lower revenues and decrease return on investment of drug development.[303] As previously noted, this approach runs counter to the current dominant strategy based on the "blockbuster" model of marketing individual drugs for use in broad populations, with target annual sales of $1 billion or more.[304] In order for PGx to be widely adopted as a drug development tool, pharmaceutical companies may have to employ new financial strategies in order to adapt to smaller per-product target markets.[305]

Despite the financial risks inherent in developing products that could result in narrowed markets, industry has begun to incorporate PGx into the drug development process. Industry's investment in PGx has been encouraged in part by FDA's moves to support more informed development of PGx-related products. In addition to the recent guidance documents pertaining to PGx data submissions and diagnostic tests, these efforts have included forming advisory groups and inter-agency collaboration, and sponsorship of conferences and symposia.[306] The Orphan Drug Act of 1983, which encourages the development of drugs for rare diseases, is another incentive for PGx drug development. This act is described in more detail in Section B of this report.

2) Co-development of PGx Diagnostics and Drugs

Many diagnostics companies perceive strong incentives to form partnerships with pharmaceutical companies to produce diagnostic and drug combination products based on the use of biomarkers. Pressure from third-party payers also may encourage co-development and co-marketing of drugs and diagnostic tests. Given that PGx-related drugs are likely to be expensive, payers may want a reliable, clinically useful diagnostic test to be available

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303 Robertson JA, Brody B, Buchanan A, Kahn J, McPherson E. Pharmacogenetic challenges for the health care system. Health Affairs 2002;21(4):155-67.

304 Bartfai T. Pharmacogenomics in drug development: societal and technical aspects. Pharmacogenomics J 2004;4(4):226-32.

305 Personalized medicine: the emerging pharmacogenomics revolution. New York, NY: PricewaterhouseCoopers, 2005. Accessed April 25, 2006. http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf.

306 Rados C. Advisory committees: critical to the FDA's product review process. Rockville, MD: US Food and Drug Administration, FDA Consumer Magazine, 2004. Accessed August 9, 2006. http://www.fda.gov/fdac/features/2004/104_adv.html.

simultaneously with the drug, allowing clinicians to target drugs to the most appropriate patients.

Collaborative arrangements are becoming more common, and it is anticipated that the number of combination products submitted for FDA review will increase.[307] FDA's 2005 concept paper on drug-diagnostic co-development outlines key considerations for industry regarding drug-device combinations. This paper suggests that industry sponsors engage FDA early to determine whether a product is likely to be part of a combination product and, if so, whether sequential or simultaneous review of the drug and diagnostic components is most appropriate.[308] After public comment, FDA plans to build upon this concept paper to develop draft guidance on drug-diagnostic co-development. The release of FDA guidelines and concept papers with clarification of issues involved in co-development should reduce some of the uncertainty of pharmaceutical companies considering parallel development of drug and diagnostic tests.

Although co-development offers potential benefits for the pharmaceutical industry, the downside is apparent.[309] Availability of a highly specific diagnostic (i.e., where a negative test rules out a genetic trait that would indicate use of a particular drug) still presents a means of narrowing a target market for a drug. In the absence of such a test, however, high levels of demand for a drug can be maintained through effective marketing. Co-development also has the potential to increase costs and time involved in bringing new therapies to market. Companies undertaking parallel product development would have to take the additional responsibility of overseeing the development of the diagnostic test. These additional costs to industry may pose disincentives, particularly for drugs that are to be narrowly targeted to patient subgroups.

PGx is a relatively new field, and industry's perceptions and investment in PGx in drug development and co-development is still evolving. Continued promulgation of guidance and other clarification from FDA, along with growing experience in developing these products, should help to reduce uncertainty for industry.

B. FDA

Through its market approval function, FDA serves as a gatekeeper of new health technologies. FDA's range of regulatory oversight affecting PGx uptake pertains to manufacturing practices, conduct of clinical trials, review of safety and efficacy data, market clearance and post-marketing surveillance. Without FDA approval of a regulated product for a particular indication, patients in the US are not able to access the product unless they participate in a clinical trial (also subject to FDA regulatory oversight) or unless they gain off-label access. PGx faces some of the same challenges as others regulated technologies and raises a few unique

[307] Annual report to Congress. Rockville, MD: US Food and Drug Administration, Office of Combination Products, 2003. Accessed March 13, 2006. http://www.fda.gov/oc/combination/Congressreport.pdf.

[308] Drug-diagnostic co-development concept paper (draft). Rockville, MD: US Food and Drug Administration, 2005. Accessed May 2, 2006. http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf.

[309] Diller W. Roche's challenging biomarker strategy. In Vivo: The Business and Medicine Report 2004:53-65.

ones, including how to regulate PGx tests that inform the use of FDA-regulated therapies but that may not be subject to FDA regulation themselves.[310]

FDA and industry interact frequently, especially leading up to key points in the product life cycle. The following section outlines FDA's main roles pertaining to PGx products, including the agency's charge to assess the safety and effectiveness of regulated new products and its development and dissemination of guidance documents for industry and other stakeholders.

1) FDA Regulation of PGx Products

Regulatory oversight of PGx testing is subject to a key distinction: whether it is done in the form of a *product* or a *service.* In the first route, a PGx test is regulated as a diagnostic test kit that is sold as an *in vitro* diagnostic device (IVD). Regulation of IVDs is primarily the responsibility of FDA. In the other route, PGx testing is provided as an "in-house" test of patient samples conducted by clinical laboratories. Although FDA has stated that it has statutory authority to regulate in-house tests, the extent of FDA's authority in this area is under debate, and FDA currently is not regulating in-house tests because of resource constraints.[311] Regulation of in-house testing by clinical laboratories is primarily the responsibility of CMS as provided in the Clinical Laboratory Improvement Amendments of 1988 (CLIA). A physician prescription is required for a clinical laboratory to perform an in-house test, which generates information—not a product — that is used by the physician for patient care decisions. This section focuses on FDA's regulatory responsibilities regarding PGx products; CMS's role in regulating in-house laboratory tests is described in Section C, below.

Within FDA, responsibilities for regulating health care products fall under the Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), and Center for Biologics Evaluation and Research (CBER). With regard to PGx diagnostics and drugs, the Office of *In Vitro* Diagnostic Device Evaluation and Safety (OIVD), within CDRH, is responsible for regulating diagnostics, whereas pharmaceuticals generally are regulated by CDER. In 1991, intercenter agreements were drafted among CDER, CBER, and CDRH to facilitate regulation of combination products, including PGx.[312,313] In response to the increasing prevalence and complexity of these products, FDA established the Office of Combination Products (OCP) in 2002. One of the purposes of OCP is to foster collaboration among the relevant FDA centers and offices involved in regulating combination products.[314] Although OCP has a broad coordinating function, primary authority for regulating any given

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310 Melzer D, Detmer D, Zimmern R. Pharmacogenetics and public policy: expert views in Europe and North America. Pharmacogenomics 2003;4(6):1-3.

311 Federal oversight of genetic tests and genetic testing laboratories. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, 2006.

312 Taulbee P. FDA proposes streamlining intercenter agreements on combo products. The Gray Sheet October 9, 2006;32(041):14.

313 As described in the October 2, 2006, Federal Register, FDA proposed the idea of eliminating the intercenter agreement between CBER and CDER, indicating that this agreement became outdated in 2003 when regulatory jurisdiction for several therapeutic biological products was transferred from CBER to CDER. The notice was open for public comment until December 1, 2006 and no final decisions have yet been issued regarding the agreement.

314 Annual report to Congress. Rockville, MD: US Food and Drug Administration, Office of Combination Products, 2003. Accessed March 13, 2006. http://www.fda.gov/oc/combination/Congressreport.pdf.

combination product rests with the individual FDA center that is assigned jurisdiction over the product (typically CDRH or CDER).[315]

a) Product Submission and Review Process

FDA regulates market entry of new IVDs via four pathways: a) premarket notification, otherwise known as the "510(k)" pathway; b) premarket approval application (PMA); c) Class I exempt; and d) humanitarian use devices. Humanitarian use devices are pursued infrequently, as these products are subject to special, rigorous regulatory requirements.

The 510(k) premarket notification process is for IVDs that are determined to be "substantially equivalent" to IVDs that are already on the market (predicate devices). FDA may request reports of clinical experience that demonstrate that a new diagnostic poses no more risk than a previously approved one. OIVD also requires submission of data indicating clinical utility.

Truly novel IVDs are subject to the more rigorous PMA process based on a review of evidence that the device is safe and effective for its intended use. For IVDs, safety is based not on contact of a device with the patient, but on the impact that information generated by the device has on patient management, for example, potential harm from false-positive or false-negative results. Since PMAs are intended to apply to truly new devices that have no predicate, their effects on human health may not be as well understood as those devices that qualify for the 510(k) pathway. As such, the evidence collection and review processes for these technologies are often more resource-intensive and time-consuming. PMAs also require a review of manufacturing processes, inspections of manufacturing facilities, an audit of clinical study sites, and comprehensive review of premarketing data.

Class I exempt IVDs are not subject to the 510(k) pathway or PMA process, but are required to have establishment registration and device listing forms on file with FDA and meet good manufacturing practices (GMP) requirements (a few Class I devices are exempt from GMP requirements). The products also must be suitable for the intended use, adequately packaged, and properly labeled. Most analyte specific agents are classified as Class I exempt. Analyte specific reagents are the active ingredients used by clinical laboratories to manufacture their in-house tests. ASRs include antibodies, receptor proteins, nucleic acid sequences and other biological or chemical reagents that are used to identify or quantify substances in biological specimens.[316] In addition to the requirements listed above, ASR manufacturers must restrict the sale of these reagents to laboratories designated as "high complexity" under CLIA.

Humanitarian use devices are for rare diseases or conditions (affecting fewer than 4,000 individuals per year) that require Humanitarian Device Exemptions (HDE). They are subject to institutional review board (IRB) approval and restrictions on their use, cost and labeling, but are exempt from demonstrating effectiveness.

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[315] Overview of the Office of Combination Products. Rockville, MD: US Food and Drug Administration, 2006. Accessed April 25, 2006. http://www.fda.gov/oc/combination/overview.html.

[316] Gutman SI. FDA's role in the regulation of in vitro diagnostic. Presentation May 10, 2003. Rockville, MD: US Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Device Evaluation and Safety, 2003. Accessed November 9, 2004. http://www.fda.gov/cdrh/oivd/presentations/051003-gutman-1.html.

FDA also regulates labeling of diagnostics and therapeutics that are marketed in interstate commerce. Drug labels describe the approved indications for use and may specify dosing, contraindications, or other important instructions. Product labeling provides clinicians with information about the use of a product as approved by FDA. The role of labeling in informing clinical practice, including some inherent strengths and weaknesses of current labeling for this purpose, and recent FDA guidance pertaining to labeling for PGx products, is described below, under Section IV, *Implementation of PGx to Improve Outcomes in Clinical Practice*.

b) Laboratory-developed PGx Tests

As described above, ASRs are the active ingredients or building blocks used in performing laboratory-developed tests, also known as "in-house" tests or "home brews." Most ASRs are produced by a diagnostics manufacturer and categorized by FDA as Class I exempt devices. Manufacturers of ASRs sold in interstate commerce to laboratories are subject to registration with FDA and compliance with good manufacturing practices (GMPs) and labeling requirements. The smaller number of ASRs that FDA designates as Class II and Class III devices, such as those involved in blood screening, are subject to more rigorous premarket review requirements. Laboratories that manufacture ASRs for their own internal use are not subject to these FDA regulations.

In contrast to their ingredient ASRs, in-house tests developed with ASRs by laboratories have traditionally not been regulated by FDA. Indeed, the laboratories must report results of their in-house tests with a standard disclaimer: "This test was developed and its performance characteristics determined by [laboratory name]. It has not been cleared or approved by the FDA."

As described below, while compliance with CLIA and FTC regulations entails certain burdens, launch of a PGx test in the form of a laboratory-developed test offers the advantage of more rapid access to market than launch of the test in the form of an IVD test kit or system that would be subject to premarket review by FDA. Disincentives for developing tests subject to the 510(k) or PMA processes may result in directing test development away from FDA oversight or attempts to market IVD test kits/test systems as ASRs.

The Food, Drug and Cosmetic Act (FDCA, as amended by the Medical Device Act and Safe Medical Devices Act of 1990) does enable FDA to have regulatory oversight over all in-house tests and their components. However, aside from the ASR oversight noted above, the agency has chosen not to exercise this authority. Some observers argue that doing so would encroach on the practice of medicine (i.e., physician prescribing of the test and use of its results in clinical decisions), which is beyond the regulatory authority of the agency.[317,318,319] Others have expressed concern that extending FDA oversight to laboratory-developed tests may slow development and result in fewer laboratories offering testing services.[320] Yet another argument is that FDA regulation of tests marketed as diagnostic test kits but not tests marketed as in-house services performed by clinical laboratories constitutes an inappropriate double standard.

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317 Borchardt PE. Pharmacogenomics: an in-house advantage? Drug Discovery Today 2006;11(12):1-3.
318 Merrill RA. Genetic testing: a role for FDA? Jurimetrics J 2000;41:63-6.
319 Federal oversight of genetic tests and genetic testing laboratories, 2006.
320 Ibid.

In the latter view, genetic tests, including some with limited predictive validity for common, complex diseases, escape having to demonstrate their clinical validity.[321]

Two draft guidances issued in September 2006 pertaining to ASRs and the new category of *in vitro* diagnostic multivariate assays clarify FDA's regulation of diagnostic testing conducted by clinical laboratories, including tests developed in-house. These guidances indicate a significant expansion of regulatory oversight of these tests, exposing them to higher standards of safety and effectiveness than they have previously been subject.

The *Draft Guidance for Industry and Food and Drug Administration Staff; Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions,* clarifies that a single ASR that is: 1) combined, or promoted for use, with another product such as other ASRs, general purpose reagents, controls, laboratory equipment, software, etc.; or 2) promoted with specific analytical or clinical performance claims, instructions for use in a particular test, or instructions for validation of a particular test using the ASR, are considered by FDA to be test systems and, thus, are not exempt from premarket notification requirements:[322]

The draft guidance appears to respond to industry efforts to market increasingly complex combinations of ASR-based products—which might be considered test kits rather than analytes—under the less demanding requirements of single ASRs. Indeed, there has been an increase in in-house tests for simultaneous detection of multiple genetic variants. A related concern involves claims for multiple functions for a single ASR when selling it to a laboratory.[323,324]

The *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff; In Vitro Diagnostic Multivariate Index Assays,* sets higher regulatory requirements for certain in-house tests that combine laboratory data with an algorithm to generate results for diagnosis and treatment. Referring to these tests as *in vitro* diagnostic multivariate index assays (IVDMIAs), the guidance states that these tests will be regulated as medical devices, classified according to their intended use and level of control necessary to assure their safety and effectiveness. In February 2007, FDA approved the first IVDMIA. MammaPrint, developed by company in The Netherlands, where the product has been on the market since 2005, is a gene expression profiling test for predicting whether an existing cancer will metastasize in women with early stage breast cancer.[325] This microarray test is intended to help clinicians more accurately predict whether

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321 Holtzman NA. FDA and the regulation of genetic tests. Jurimetrics J 2000;41:53-62.

322 Draft guidance for industry and FDA staff. Commercially distributed analyte specific reagents (ASRs): frequently asked questions. Rockville, MD: US Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety, 2006. Accessed September 8, 2006. http://www.fda.gov/cdrh/oivd/guidance/1590.pdf.

323 Center sees "new era in oversight" of genetic tests in two new FDA draft guidances. Washington, DC: The Genetics and Public Policy Center, 2006. Accessed March 8, 2007. http://www.dnapolicy.org/news.release.php?action=detail&pressrelease_id=56.

324 Gibbs JN. Regulations & standards: the past, present, and future of ASRs. Medical Devicelink, 2003. Accessed March 8, 2007. http://www.devicelink.com/ivdt/archive/03/11/012.html.

325 FDA clear breast cancer specific molecular prognostic test. Rockville, MD: US Food and Drug Administration, 2007. Accessed February 27, 2007. http://www.fda.gov/bbs/topics/NEWS/2007/NEW01555.html.

existing cancer will metastasize.[326] It is currently unclear what proportion of PGx tests will fit within the IVDMIA category.

The draft guidance notes that the manufacture of an IVDMIA involves steps that are not synonymous with the use of ASRs to make in-house tests with "ordinary expertise and ability." Whereas most ASRs are designated as Class I devices, usually exempt from premarket review, most IVDMIAs will be subject to higher evidence requirements.[327] Class II devices typically are subject to the 510(k) premarket notification process, whereas Class III devices are subject to the more rigorous PMA process. The guidance makes a key distinction for which type of premarket notification will be required based on the intended use of an IVDMIA:

> "We believe most IVDMIAs will be either class II or III devices. For example, a device intended as an indicator of a patient's risk of cancer recurrence may be a class II device, while the same device intended to predict which patients should receive chemotherapy might require Premarket Approval."

As a result of these guidances, more complex in-house tests will be subject to the greater scrutiny of premarket review via the 510(k) or PMA processes.

Exhibit 3. The Case of Oncotype DX™

Onco*type* DX™ (Genomic Health, Inc.) is an example of the type of diagnostic test that would fall into the IVDMIA category as defined in the draft guidance. Designed to predict the risk of recurrence in women with early-stage breast cancer, this test is being used in a new treatment study, the Trial Assigning Individualized Options for Treatments (Rx), or TAILORx, sponsored by NCI and launched in May 2006. TAILORx uses the Onco*type* DX™ test to measure the expression of 21 genes in breast tumors, estimating the patient's risk of cancer recurrence. This measurement is reported to be more effective than current tests based on the size and grade of the tumor, and could help clinicians to individualize treatment plans for patients.[328] The benefit of adding chemotherapy to standard radiation and hormone therapy in these patients varies and may not be substantial. Thus, a patient with a low chance of breast cancer recurrence, as might be predicted using the Onco*type* DX™ test, may not need to undergo unnecessary chemotherapy in addition to receiving standard therapy. Given the toxicity of chemotherapy, reducing unnecessary treatment could improve quality of life for breast cancer survivors.[329] While the test has not been approved by FDA to date, it is already covered by some health plans for use in clinical practice.[330,331]

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326 About MammaPrint. Amsterdam, The Netherlands: Agendia, 2007. Accessed February 27, 2007. http://www.agendia.com/index.php?option=com_content&task=view&id=6&Itemid=29.

327 Draft guidance for industry, clinical laboratories, and FDA staff: in vitro diagnostic multivariate index assays. Rockville, MD: US Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety, 2006. Accessed September 8, 2006. http://www.fda.gov/cdrh/oivd/guidance/1610.pdf.

328 Personalized treatment trial for breast cancer launched. Bethesda, MD: National Institutes of Health, 2006. Accessed June 6, 2006. http://www.nih.gov/news/pr/may2006/nci-23.htm.

329 Paik S, Tang, G, Shak S et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor positive breast cancer. J Clin Oncol 2006;24(23):3726-34.

330 Comments on NHIC on the LCD for the Oncotype DX test. Bethesda, MD: Association for Molecular Pathology, 2005. Accessed August 9, 2006. http://amp.org/PRC/OncotypeDX.doc.

331 TA 6.35 Oncotype DX recurrence score assay for predicting breast cancer recurrence. Wellesley, MA: Harvard Pilgrim Health Care, 2005. Accessed August 9, 2006. http://www.harvardpilgrim.org/pls/portal/docs/PAGE/PROVIDERS/MEDMGMT/STATEMENTS/ONCOTYPEDX_POLICY7.05.PDF.

The TAILORx trial is intended to enroll more than 10,000 patients, who will be followed periodically for 20 years after completion of the study. Investigators will analyze correlations between results of assays (including the Onco*type* DX™ test) of tissue collected from patients prior to study enrollment and their outcomes during follow-up.[332]

2) FDA Guidance for PGx Products

The emergence of PGx focuses attention on the adequacy of regulation of products whose use and effects are associated with genetic differences. FDA has acknowledged the need to adapt its policies and processes in recognition of this emerging field and is beginning to respond.[333] FDA recently generated two guidance documents to facilitate efficient data submissions and reviews of PGx products. The *Pharmacogenomic Data Submissions* guidance, issued in March 2005, pertains primarily to the therapeutic side of PGx. It is intended to facilitate scientific progress in PGx and the use of PGx data in drug development. The guidance provides recommendations to sponsors with new drug applications (NDAs) and biologics license applications (BLAs) on: 1) when to submit PGx data to FDA during the associated drug or biological drug product development and review processes, 2) what format to use and content to include when submitting PGx data, and 3) how and when data will be used in regulatory decision-making.[334]

Many companies had been concerned that FDA might misinterpret use of exploratory, non-validated genomic biomarkers, causing delays in drug development, or request additional clinical trials or put clinical trials on hold. The 2005 *Pharmacogenomic Data Submissions* guidance (along with its draft version issued in 2003) reduced uncertainty regarding how the agency would handle exploratory genomic data obtained during the new drug development process. However, given the potential impact of PGx and heightened interest in drug safety, it suggests that such data could be mandatory for new drug approval in the future.[335]

Another draft guidance, *Pharmacogenetic Tests and Genetic Tests for Heritable Markers,* issued in February 2006, pertaining to PGx testing is intended to shorten product development and review timelines, facilitate rapid transfer of new technology to clinical diagnostic laboratories, and encourage informed use of PGx and genetic diagnostic devices. The guidance provides recommendations to sponsors and FDA reviewers in preparing and reviewing 510(k) and PMA submissions for PGx and other genetic tests.[336] Although FDA has ensured that this draft guidance allows room for growth and development of the PGx field, it may have important

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[332] Phase III randomized study of adjuvant combination chemotherapy and hormonal therapy versus adjuvant hormonal therapy alone in women with previously resected axillary node-negative breast cancer with various levels of risk for recurrence (TAILORx trial). Bethesda, MD: National Cancer Institute, 2007. Accessed March 1, 2007. http://www.cancer.gov/search/viewclinicaltrials.aspx?cdrid=472066&version=healthprofessional&print=1.

[333] Phillips KA, Van Bebber SL. Regulatory perspectives on pharmacogenomics: a review of the literature on key issues faced by the United States Food and Drug Administration. Med Care Res Rev 2006;63(3):301-26.

[334] Guidance for industry: pharmacogenomic data submissions. Rockville, MD: US Food and Drug Administration, 2005. Accessed May 2, 2006. http://www.fda.gov/cber/gdlns/pharmdtasub.htm.

[335] Borchardt PE. Pharmacogenomics: an in-house advantage? Drug Discovery Today 2006;11(12):1-3.

[336] Draft guidance for industry and FDA staff: pharmacogenetic tests and genetic tests for heritable markers. Rockville, MD: US Food and Drug Administration, 2006. Accessed April 25, 2006. http://www.fda.gov/cdrh/oivd/guidance/1549.pdf.

implications for the types of data that are made available for PGx products, the timeline from approval to adoption, and patient access.[337]

PGx is likely to elicit additional guidance and other measures as the field evolves.[338] FDA is currerntly engaged in issues relevant to PGx, including the extent to which genetic data may be required in the drug approval process, whether there will be further review of previously approved drugs as relevant genetic data become available, the circumstances under which testing may be required before or after initiation of drug therapy, the co-marketing/co-development and labeling of PGx-based tests and drugs, and determining the relevance of the Orphan Drug Act to PGx.[339,340,341,342,343]

3) Gap between PGx Test Approval and Clinical Practice

Aside from the intricacies of FDA's role as market gatekeeper for PGx products, the agency's requirements and actions—or the lack thereof —influence the ways in which marketed PGx technologies are used in clinical practice. For example, FDA approval of a PGx test does not necessarily result in dosing guidelines for the accompanying therapy. One example arises with FDA approval of Roche's AmpliChip for genotyping of the CYP2D6 and CYP2C19 variants, which affect metabolism of antidepressants, antipsychotics, immunosuppressives and anticancer drugs. As neither Roche nor FDA has provided recommendations for appropriate drug dosing, the clinical utility of the chip is not well defined. Clinical trials of PGx diagnostics and drug responses across patient subgroups could provide the basis for such recommendations, yet few such trials are underway.

In another current instance, FDA approved a labeling change for the anticancer drug irinotecan (Camptosar), to include information about the relationship between UGT1A1*28 polymorphisms and the risk of ADRs.[344] However, the revised label does not include a requirement or recommendation for UGT1A1 testing due to an insufficiency of data to support a recommendation on dose schedules by genotype.[345] In lieu of recommended dosing schedules, the FDA-approved labeling states that "a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele … However, the precise dose reduction in this population is not known, and subsequent dose modifications should be considered based on individual patient tolerance to

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337 Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery 2004;3(9):763-9.

338 Melzer D, Detmer D, Zimmern R. Pharmacogenetics and public policy: expert views in Europe and North America. Pharmacogenomics 2003;4(6):1-3.

339 Robertson JA, Brody B, Buchanan A, Kahn J, McPherson E. Pharmacogenetic challenges for the health care system. Health Aff (Millwood) 2002;21(4):155-67.

340 Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. Pharmacogenomics J 2002;2(1):20-4.

341 Salerno RA, Lesko LJ. Pharmacogenomics in drug development and regulatory decision-making: the genomic data submission (GDS) proposal. Pharmacogenomics 2004;5(1):25-30.

342 Eisenberg RS. Will pharmacogenomics alter the role of patents in drug development? Pharmacogenomics 2003;3(5):571-4.

343 Issa AM. Pharmacogenomic profiling in post-marketing surveillance: prospects and challenges. Pharmacogenomics 2003;4(5):647-55.

344 Haga SB, Thummel KE, Burke W. Adding pharmacogenetics information to drug labels: lessons learned. Pharmacogenetics and Genomics 2006;16:847-54.

345 Haga SB 2006.

treatment."[346] The subcommittee reviewing the product further noted that, "although there is indication to start with a lower dosage, it is not necessarily an indication that sensitive patients will do well with this dosage."[347] This example illustrates that PGx testing can identify patients who are likely to respond differently to particular drugs and can indicate that the dose of a drug should be different than is typical, but that testing does not necessarily translate into dosing instructions. As such, patients will have to be monitored and have their dosing adjusted empirically.

In the absence of relevant clinical data, it is not apparent that FDA has the ability or responsibility to insert recommendations concerning PGx test results and drug dosing into product labels. Such recommendations may need to come from medical professional organizations in the form of practice guidelines, although they too would seek adequate evidence upon which to base such guidelines.[348,349] Some have suggested that FDA seek more input from academic experts, practicing physicians, and pharmaceutical companies to translate findings from large prospective studies into dosing guidelines for use in clinical practice.[350,351] The broader gatekeeping role of guideline developers for PGx is described in Section D, below.

C. CMS and Other Third-party Payers

The ability to obtain favorable reimbursement is widely recognized as being critical to the success of innovative health technologies. Once new PGx products reach the market, they face payer gatekeepers such as Medicare, Medicaid, commercial payers, and intermediaries such as pharmaceutical benefit managers (PBMs). A commercial publication in this market observes:

> "For industry, there's no point in investing in developing personalized drug therapies if payors won't cover them. One thing is sure: manufacturers better not follow FDA too far down the Critical Path to personalized medicine without finding the right formula for payment at the end of the road."[352]

The following sections describe the importance of reimbursement for the future of PGx and outline reimbursement challenges to PGx in particular.

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346 NDA 20-571/S-024/S-027/S-028. Camptosar®(irinotecan HCl). Hepatic dysfunction, pancreatitis, UGT1A1. July 21, 2005. Final label. Rockville, MD: US Food and Drug Administration, 2005. Accessed August 30, 2006. http://www.fda.gov/cder/foi/label/2005/020571s024,027,028lbl.pdf.

347 Clinical Pharmacology Subcommittee, Advisory Committee for Pharmaceutical Science. Final report of meeting, November 3-4, 2004. Rockville, MD: US Food and Drug Administration, 2004. Accessed August 30, 2006. http://www.fda.gov/OHRMS/DOCKETS/ac/04/minutes/2004-4079M1.htm.

348 Jain KK. Applications of AmpliChip CYP450. Mol Diagn 2005;9(3):119-27.

349 Need AC, Motulsky AG, Goldstein DB. Priorities and standards in pharmacogenetic research. Nature Genetics 2005;37(7):671-81.

350 Transcript of ninth meeting - March 27, 2006. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, 2006. Accessed May 4, 2006. http://www4.od.nih.gov/oba/SACGHS/meetings/March2006/transcripts/FullDayTranscript03-27.pdf.

351 Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews 2004;3:763-9.

352 Rawson K. Reimbursing designer drugs. The RPM Report 2006;1(10):19-24. Norwalk, CT: Windhover Information, Inc.

1) Overview of Reimbursement in the US

Generally, the term "reimbursement" encompasses three main components, including coverage, coding and payment. Coverage describes whether a third-party payer will pay for a particular item or service under benefits provided to its beneficiaries. Coding refers to the alphanumeric systems used to identify items and services and to which payment levels are assigned. Payment refers to the compensation provided by third-party payers, as well as any patient share of the cost, to clinicians, health care facilities, or other providers of particular items or services.

In the US, the two main categories of third-party payers are public payers, including Medicare, state Medicaid programs, the VA, and TRICARE (Department of Defense); and private payers such as insurance companies and commercial health plans. A brief description of these payers with regard to their gatekeeping roles for PGx is provided below.

a) Medicare

Administered by CMS, Medicare is the largest single health care payer in the US and has substantial influence in the health care market. CMS coverage and payment policies for the Medicare program can affect clinicians' willingness to provide PGx products, Medicare beneficiaries' access to them, and industry's interest in developing them. CMS coverage policies and payment levels also are highly influential to other public and private sector payers. For instance, recent reports indicate that Medicare's payments for diagnostic tests, which has not updated for inflation in 13 of 15 consecutive years through 2004, have fallen short of reflecting their value or being adjusted over time for inflation, and that because many other payers follow Medicare's lead in setting payment levels, these shortcomings often carry over to reimbursement rates of other third-party payers and covered patients.[353,354,355] In recognition of the influence that Medicare has over other payers, SACGHS suggested in its February 2006 report, *Coverage and Reimbursement of Genetic Tests and Services*, that it may be inappropriate for private payers to follow Medicare's lead in the area of genetic testing.[356]

Depending on the testing circumstances, Medicare coverage of PGx tests may be limited by statute that permits coverage only for items or services that are "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." Accordingly, the Medicare statute does not provide coverage for tests – genetic or otherwise – used for screening purposes, i.e., in patients without signs, symptoms, complaints or personal history of disease or injury, unless specifically authorized by law.

In order for Medicare to cover screening or preventive interventions, Congress must pass new legislation, as it has in such instances as screening mammography, prostate specific antigen (PSA) testing for prostate cancer screening, and bone densitometry for those at risk for osteoporosis. Generally, PGx tests (e.g., tests for HER-2/neu over-expression) to identify which patients among those known to have a particular condition are likely to respond to treatment are eligible for coverage under Medicare. However, PGx tests can be performed in the absence

353 Medicare reimbursement for clinical laboratory services. Washington, DC: American Clinical Laboratory Association, 2004. Accessed April 26, 2006. http://www.clinical-labs.org/issues/reimbursement/index.shtml.

354 Goodman C 2005.

355 Ibid.

356 Coverage and reimbursement of genetic tests and services, 2006.

of an existing condition for which a drug would need to be prescribed but for which advance knowledge of the test results would be beneficial (e.g., for emergency situations where it could be detrimental to the patient's health to delay administration of the drug, but the risk of an ADR is high and presence of the ADR-associated gene variant could be discerned easily with PGx testing). This screening application of PGx generally would not be covered by Medicare, as the test result generally would not inform a decision regarding how to treat a patient. Unless legislation is passed, these types of screening or preventive applications of PGx may encounter challenges in obtaining Medicare coverage.

Rather than relying on Congress to pass legislation on an ad hoc basis, adding prevention as a Medicare benefit category would enable HHS to develop coverage and payment policies for particular services in a more systematic manner, drawing on the existing processes and expertise at CMS. In its 2006 *Coverage and Reimbursement of Genetic Tests and Services* report, SACGHS recommended that Congress add a preventive services benefit category. Establishing a Medicare benefit category for preventive services would not only affect use of PGx technologies, but would have parallel and downstream effects on use of other preventive, diagnostic, and therapeutic services. Although there is growing awareness of the clinical value of providing a benefit category for screening and preventive services, Congress and CMS would need to consider strategies for financing this expanded access to care prior to implementation. Also, whether by Medicare or other payers, providing clear policies and criteria regarding when tests are indicated for screening/primary prevention and diagnosis, respectively, may reduce uncertainty on the part of providers, manufacturers and patients.

b) Private Payers

As noted above, many private payers monitor coverage and payment policies of Medicare, and often develop ones that are similar to those of Medicare. However, private payers often have their own processes for evaluating new technologies and establishing reimbursement, including both internal and external technology assessments. Although many payers' coverage policies are not publicly available, some publish clinical policy bulletins on their websites.

With regard to PGx products, Aetna currently has three relevant policies: one on Herceptin, one on tumor markers, and a third focused on other PGx testing services. Aetna's 2005 clinical policy bulletin regarding Herceptin states that the use of this drug is medically necessary for certain breast cancer patients with over-expression of the HER-2/neu protein.[357] Aetna's policy bulletin on tumor markers considers Oncotype Dx to be medically necessary in women whose breast tumor is HER2 receptor negative or HER2 receptor positive and less than 1 cm in diameter, in addition to several other criteria.[358] Various findings from RCTs and other studies are included in these bulletins to support the clinical value and coverage of Herceptin and Oncotype Dx. In contrast to these two policy bulletins, a 2006 Aetna clinical policy bulletin on PGx testing found that both CYP450 polymorphism genotyping and the Invader UGT1A1 molecular assay (for determining optimal dosing of the drug irinotecan for patients with colorectal cancer) were still in the investigational or experimental phases, and that the clinical

[357] Clinical policy bulletins: Herceptin (trastuzumab). Number 0313 (revised). Hartford, CT: Aetna, Inc., 200. Accessed May 2, 2006. http://www.aetna.com/cpb/data/CPBA0313.html.

[358] Clinical policy bulletins: Tumor markers. Number 0352. Hartford, CT: Aetna, Inc., 2006. Accessed March 21, 2007. http://www.aetna.com/cpb/medical/data/300_399/0352.html.

value of these tests has not been demonstrated.[359] To support this conclusion, the bulletin cited conflicting evidence from recent studies and cited the need for additional investigation. Regarding the Invader UGT1A1 molecular assay, the bulletin noted that the product labeling for the drug irinotecan does not specify that UGT1A1 status should be assessed prior to prescription of irinotecan, as described above, which highlights the importance of product labeling for PGx products in coverage determinations.

PGx may pose a particular challenge to health plans' coverage of prescription drugs. Health plans select the prescription drugs they will cover under their plan based upon the drugs' efficacy, safety and cost-effectiveness. Drugs selected for inclusion in the plan's drug formulary are often assigned different tiers, with higher levels of cost sharing associated with the higher tiers. Drugs that are not covered by a health plan ("non-formulary") are subject to greater cost sharing or not covered at all. In certain plan members, the preferred formulary drug may be less effective or more toxic than a non-formulary or higher tiered drug, based on the results of a PGx test. These plan members may be responsible for a greater share of the costs to ensure that they are getting the safest and most effective drug based on their genetic makeup. This could raise concerns about appropriate access and genetic discrimination. Such situations may become more common as more PGx tests become available for clinical use. Health plans will need to decide how they will respond when these situations arise.

Recommendation 9

In instances where a validated PGx test is available to guide therapeutic decision-making, health plans, including Medicare prescription drug plans, should cover the most clinically appropriate drug as indicated by PGx test results.

c) Health Technology Assessment Groups

Health technology assessment (HTA) involves assessing the strength of evidence and conducting systematic reviews and other analyses of clinical and economic data for new or existing health technologies. Although the results of HTAs are not used exclusively to inform reimbursement decisions, they do provide important information for Medicare and private payers during coverage deliberations. High-profile breakthrough technologies tend to be subject to HTA, particularly if they have a large potential impact on health or costs. While such impacts may be direct, they also may be indirect, such as for PGx when the results of a diagnostic test have the potential to increase or decrease the use of costly downstream interventions.

HTAs may be conducted internally by a payer or an affiliated analytical unit, commissioned from an outside source, or some combination of these. When CMS requires HTAs to inform a Medicare coverage determination, it has the option of requesting an evidence review from the Agency for Healthcare Research and Quality (AHRQ). For example, CMS commissioned AHRQ to conduct a comparative clinical and cost-effectiveness study regarding screening immunoassay fecal-occult blood testing for a coverage review in 2003.[360] Private payers use varying strategies for completing or commissioning HTAs. Although many private payers do

[359] Clinical policy bulletins: pharmacogenetic testing. Number 0715 (revised). Hartford, CT: Aetna, Inc., 2005. Accessed May 2, 2006. http://www.aetna.com/cpb/data/CPBA0715.html.

[360] Decision memo for screening immunoassay fecal-occult blood test (CAG-00180N). Baltimore, MD: Centers for Medicare and Medicaid Services, 2003. Accessed March 2, 2007. http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=87.

not have sufficient internal resources or expertise to conduct formal, comprehensive reviews of new technologies, many larger plans and networks such as Aetna, CIGNA, Harvard Community Health Plan, HealthPartners of Minnesota, United Healthcare, WellPoint, Highmark and various Blue Cross and Blue Shield plans have extensive internal functions for this purpose. To supplement these assessments, many private payers also purchase assessments from HTA vendors such as ECRI or HAYES, Inc.

Another influential HTA program is the joint Technology Evaluation Center (TEC) of the Blue Cross Blue Shield Association (BCBSA) and Kaiser Permanente.[361] Assessments from BCBSA TEC are publicly available and often are nationally visible, serving as an important source of information for Blue Cross and Blue Shield plans and other payers.[362] Their purpose is to provide health care decision-makers with, "timely, objective and scientifically rigorous assessments that synthesize the available evidence on the diagnosis, treatment, management, and prevention of disease."[363] A medical advisory panel comprising independent, nationally recognized experts in HTA, clinical research and medical specialties, has scientific accountability for all TEC assessments. Although TEC reports do not generate coverage decisions and are not binding on Blue Cross and Blue Shield plans, individual Blue Cross and Blue Shield plans and other private payers frequently use findings from these reports in making coverage decisions.

2) Importance of Reimbursement for Adoption and Diffusion of PGx

As described above, achieving third-party coverage and adequate payment has been essential to ensuring patient access to many new health care technologies. Just as achieving adequate payment can speed adoption and use of a product, failure to do so can pose a serious challenge to product access. The prospect of failing to achieve adequate reimbursement may discourage technological innovation, which ultimately limits both patient and provider access to new health technologies.[364] Reimbursement will play a critical role in the future of PGx, affecting not only innovation on the part of manufacturers, but influencing provider adoption and patient access, among other aspects as described below.[365,366]

a) Influence on Innovation

Although the reimbursement policies themselves are usually made at the time of or following their appearance on the market, the potential impacts of these policies are increasingly weighed by manufacturers and other sponsors and investors earlier in the product life cycle. As is so for other innovative health care products, the prospects for reimbursement, including the potential extent of covered indications and payment levels for these, are key considerations of manufacturers when determining whether to invest in development of new PGx products. To the extent that manufacturers expect that coverage will be difficult to obtain or that payment

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361 The Blue Cross and Blue Shield Association Technology Evaluation Center has been in place since 1985. Its collaborative relationship with Kaiser Permanente began in 1993.

362 Technology Evaluation Center. Chicago, IL: Blue Cross Blue Shield Association, 2007. Accessed March 2, 2007. http://www.bcbs.com/tec/.

363 Technology Evaluation Center. Chicago, IL: Blue Cross Blue Shield Association, 2007. Accessed March 2, 2007. http://www.bcbs.com/tec/.

364 Coverage and reimbursement of genetic tests and services, 2006.

365 Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.

366 Phillips KA 2004.

levels are likely to be inadequate, manufacturers may determine that investment in the development of new PGx products is not a good return on investment. If innovation of PGx products lags due to unfavorable reimbursement, providers and patients ultimately have access to fewer new PGx products. On the other hand, favorable prospects for reimbursement can help to attract investment in PGx product development, speed adoption by providers, and accelerate product demand.

Some have suggested reimbursing health technologies such as PGx according to the value they provide, taking into account clinical as well as economic benefits. If payment systems were changed to reflect value, this might influence the incentive structure for development and use of PGx, as members of industry may be more confident about receiving favorable reimbursement for newly developed products. However, any changes to reflect a value-based approach may require changing the broader system for reimbursing health care.

b) Influence on Provider Adoption

In addition to the availability of new PGx products, provider adoption depends on at least two important factors. First, although third-party payers specify that billing patterns and provider charges are the main inputs into payment level determinations, providers often report that payments are not adequate to cover the cost of providing the service.[367] To the extent that reimbursement is insufficient to cover the costs of a procedure, this can discourage provider adoption of a new health care technology. If providers do perform a service that is reimbursed inadequately, patients may be responsible for paying the difference between the provider's fee and the insurance payment, or providers may take the loss.

c) Influence on Patient Access

Aside from matters of innovation or provider adoption, third-party payer reimbursement decisions directly influence patient access in other ways. If a PGx product is not covered by a health plan, patients may not be able to access the product unless they choose to pay out-of-pocket for their care. Similarly, if a PGx product is covered but inadequately reimbursed, patients may have to take on a higher share of the cost, e.g., via a co-payment, in order to receive care. These financial hurdles may result in stratification of patient access to PGx tests and drugs according to ability to pay.[368]

Once coverage for a particular PGx product has been established, reimbursement still may influence patient access to care. For instance, some predictive genetic testing (i.e., to identify genes that cause or increase the risk of certain diseases or condition) is intended to be accompanied by genetic counseling to ensure that patients understand the meaning of their test results. However, genetic counselors, particularly non-physician ones, often report difficulty in obtaining adequate reimbursement.[369] Many PGx tests are likely to be complex and require careful interpretation and communication to patients, raising similar concerns. If their time or expertise is not adequately reimbursed, clinicians who are already under pressure to see many

[367] Coverage and reimbursement of genetic technologies. Issue brief. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, 2004.

[368] Ibid.

[369] Coverage and reimbursement of genetic tests and services, 2006.

patients may be unwilling or unable to devote the time needed to explain PGx test results to patients, and genetic counseling may not be widely or equitably available.

For PGx technologies with high unit (per patient) costs or high aggregate (population) costs, payers may institute additional cost-sharing or cost-control strategies.[370] This could discourage patients with insufficient financial resources from undergoing PGx testing. Payers also may take steps to control the use of PGx products, by granting coverage only for a tightly defined set of indications or requiring prior authorization for using the technologies. The use of these mechanisms may serve to limit patient access to PGx products.

d) Role of Coding

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), is the official system in the US for assigning codes for patient diagnoses and conditions and hospital procedures. The Healthcare Procedural Coding System (HCPCS) is used for reporting medical, surgical and diagnostic procedures and services (including clinical laboratory services), durable medical equipment, orthotics, prosthetics and medical supplies.

HCPCS has two main levels. Level I comprises the set of Current Procedural Terminology (CPT) codes, which describe medical, surgical and diagnostic services.[371,372] Level II HCPCS codes were established primarily for submitting claims for a variety of services, supplies, and equipment covered by Medicare and other payers that are not identified by CPT-4 codes. These include durable medical equipment, prosthetics, orthotics, and supplies (DMEPOS) when used outside a physician's office, and ambulance services. HCPCS codes are assigned payment levels by each payer. The existence of a code does not determine whether any third-party payer covers or reimburses for an item or service. Issues regarding the use of coding for determining medical necessity are discussed below.

3) Potential Reimbursement Challenges for PGx

The prospects for reimbursement are mediated by various factors, including the need to demonstrate clinical value of PGx, satisfy medical necessity requirements, and manage off-label use. These are described briefly, below.

a) Demonstrating Clinical Value of PGx

In determining whether coverage is appropriate for a new PGx technology, third-party payers may consider the clinical value of the technology. For example, a new test may gain FDA approval based on evidence showing that it has high sensitivity and high specificity for identifying a genetic trait that is known to affect the metabolism of a particular drug. However, when reviewing a new diagnostic test, payers increasingly are moving from seeking evidence only about test accuracy to seeking evidence linking test results to their impact on diagnosis, therapeutic selection, health outcomes, and sometimes economic endpoints. Payers are more

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370 Goodman C 2005.

371 CPT process – how a code becomes a code. Chicago, IL: American Medical Association, 2007. Accessed February 27, 2007. http://www.ama-assn.org/ama/pub/category/3882.html.

372 HCPCS general information – overview. Baltimore, MD: Centers for Medicare and Medicaid Services, 2007. Accessed February 27, 2007. http://www.cms.hhs.gov/MedHCPCSGenInfo/.

often seeking such evidence in the form of controlled clinical trials or other rigorous studies comparing the health outcomes or other impacts of a new test to those of the standard of care. In its 2006 *Coverage and Reimbursement of Genetic Tests and Services* report, SACGHS recommended that the Secretary of HHS convene a group of experts to review the evidence on a genetic test's analytical and clinical validity and clinical utility in order to identify areas of adequacy and inadequacy.[373]

Establishing causal effects of diagnostics, particularly on health outcomes, can be challenging and sometimes impractical, as various factors (e.g., use of multiple diagnostics, physicians' desire to rule out conditions and multiple treatment options) can confound these downstream effects. Further, payers are increasingly interested in evidence acquired in routine or community practice, in addition to evidence gathered under more controlled conditions such as in premarket clinical studies conducted for gaining FDA approval. This is particularly the case when skill levels, experience, or care setting may affect the accuracy of a technology, or when the risk profile of a community-based population differs enough from the risk profile of the more selected or narrowly defined populations typically tested in premarket trial to change the test's predictive value.

A current example of payer evidence requirements for demonstrating clinical value is the Aetna policy for AmpliChip. The policy calls for randomized controlled trials to determine if testing with AmpliChip will result in lower incidence of ADRs by detecting patients with CYP2D6 and CYP2C19 mutations, and that AmpliChip should be compared to standard methods of therapeutic drug monitoring. The policy for the Invader UGT1A1 test notes that "the clinical value of this testing (i.e., whether testing will lead to better health outcomes) has yet to be established by prospective, randomized, controlled trials."[374]

b) Satisfying Medical Necessity Requirements

Although coverage policies designate the health care products and services for which a payer will reimburse a health care provider, payers reserve the right to determine whether the given product or service is medically necessary for a given patient. This represents another important gatekeeping function.

Determinations of medical necessity generally are based on a patient's diagnosis or condition and relevant coding. Definitions of medical necessity vary among payers, but generally include provisions that services should: 1) be appropriate; 2) alleviate a problem involving a patient's health, functioning or well-being; 3) be concordant with accepted medical practice; and 4) not be investigational, experimental or educational.[375] Medical necessity determinations remain controversial, due, in part, to variations in health plan's medical necessity criteria and a perceived lack of transparency in their application of the criteria.[376]

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[373] Coverage and reimbursement of genetic tests and services, 2006.

[374] Clinical policy bulletins: pharmacogenetic testing. Number 0715 (revised). Hartford, CT: Aetna, Inc., 2005. Accessed May 2, 2006. http://www.aetna.com/cpb/data/CPBA0715.html.

[375] Bare J. Making sense of health plan denials. Fam Pract Manag 2001;8:39-42.

[376] Singer SJ, Bergthold LA. Prospects for improved decision making about medical necessity. Health Affairs 2001;20(1):200-6.

Many emerging technologies, such as gene-based diagnostic tests involving multiple biomarkers and PGx therapies indicated by results of genetic tests, challenge conventional interpretations of medical necessity, and the pace of PGx innovation can challenge existing mechanisms for determining medical necessity. As a result, PGx technologies may encounter barriers to coverage and payment. Since medical necessity determinations often start with codes appearing on billing claims, coding systems may need to be revised in order to enable providers to code PGx products more accurately. In response to concerns that existing CPT codes were not sufficiently detailed to describe genetic tests, a new set of modifier codes for molecular genetic tests was added for use with generic CPT codes, effective in 2005. Though not affecting payment levels assigned to these tests, these modifiers are intended to enable providers to submit more complete and specific information in their claims about the purpose of these tests.[377,378] It is not yet apparent whether these genetic modifiers for CPT codes are adequate for their intended purpose of enabling more accurate billing.

Among other groups, the Institute of Medicine has expressed that the ICD-9-CM coding system may no longer be appropriate for determining medical necessity for certain health services. In particular, some suggest that ICD-9-CM may be too outdated to respond adequately to the emerging needs of payers and providers in an environment of rapid technological evolution.[379] Section 942 of Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA) acknowledged recommendations to replace the 23-year-old ICD-9-CM coding system with ICD-10, a potentially more effective system for determining medical necessity and accommodating codes for new technologies such as PGx.[380]

c) Potential for Off-label Use

For most pharmaceutical products, payers generally reimburse for covered services that are provided in accordance with product labeling to treat FDA-approved indications. Payers also reimburse for many off-label indications, particularly for treating certain forms of cancer. With few PGx products having reached the market to date, the extent to which PGx information will be specified as part of product labeling for new drugs is uncertain. For instance, if a particular drug is most effective in a population of patients with a certain genotype, it is not apparent whether labeling will specify that a PGx test must be conducted prior to administration of the drug. To the extent that PGx tests are required as part of drug labeling, use of the drug without the PGx test would constitute off-label use. Although payers often cover off-label use, this is a more uncertain and risky payment avenue for new products.[381] At least until an off-label use moves into the medical mainstream, as many have, providers using PGx products for off-label indications are at risk for receiving no payment or inadequate payment, or patients may have to pay out-of-pocket for the PGx product. If this were to occur, provider adoptions and patient access to the product could be affected.

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377 Ibid..

378 Miller L. Chapter and verse on next year's CPT code changes. CAP Today; December 2004. Accessed February 3, 2007. http://www.cap.org/apps/docs/cap_today/feature_stories/1204cptchanges.html.

379 Wolman DM, Kalfoglou AL, Leroy L. Medicare laboratory payment policy now and in the future. Washington, DC: Institute of Medicine, Committee on Medicare Payment Methodology for Clinical Laboratory Services, 2000. Accessed May 4, 2006. http://www.iom.edu/report.asp?id=5547.

380 Ivor L. The Medicare Modernization Act: what's in it for IVDs. IVDT 2004;4(1):18.

381 Off-label use of anticancer therapies: physician prescribing trends and the impact of payer coverage policy. Washington, DC: Biotechnology Industry Organization, 2005. Accessed April 26, 2006. http://www.bio.org/speeches/pubs/CovanceReport.pdf.

4) CMS Regulatory Responsibilities: CLIA

In addition to its pivotal role in reimbursement, CMS has regulatory responsibilities for certain types of diagnostic tests under the Clinical Laboratory Improvement Amendments Act of 1988 (CLIA). CLIA gives CMS the authority to regulate in-house testing by clinical laboratories. As such, CLIA has particular relevance for the diagnostic portion of PGx products.

CLIA established standards for quality assurance, record maintenance, and proficiency testing of personnel for all clinical laboratories in the nation.[382] CMS has oversight of two main requirements for testing services under CLIA: 1) registration with the CLIA program, and 2) certification by an approved accreditation body. Certification is intended to ensure that a clinical laboratory meets certain minimum levels of quality, i.e., personnel qualifications, quality control procedures, and proficiency testing.[383] CLIA requirements for laboratory certification depend on the complexity of the tests performed. There are specific requirements for such specialty areas as microbiology and cytogenetics (the study of chromosomes and the diseases caused by numerical and structural chromosomal abnormalities), though genetic testing is not recognized as a CLIA specialty area.[384] In an example of the interactions between gatekeepers, FDA has been involved with CLIA since 2000, when it took over the responsibility of categorizing the complexity of certain diagnostic tests.[385] The tests are also subject to relevant Federal Trade Commission (FTC) regulations for marketing.

CLIA requirements for in-house laboratory testing are generally less rigorous than FDA requirements of the 510(k) and PMA premarket review process. CLIA requires that a laboratory demonstrate the analytical validity and reliability of its in-house tests, but does not require demonstration of the clinical validity or utility of these tests. This is in contrast to FDA requirements for IVDs, which must submit data indicating all four of these attributes.[386]

Given the role of third-party payers in determining reimbursement and CMS's additional role in regulation of in-house diagnostic tests, it is clear that payers are important gatekeepers with significant influence over the trajectory of PGx and other medical technologies.

D. Clinical Practice Guideline Developers

Once PGx products reach the market, another set of gatekeepers mediating their adoption and diffusion are clinical practice guideline developers. These gatekeepers interpret medical evidence, apply clinical judgment, and present it in actionable recommendations for use by providers in patient care. As described in more detail in Section IV, providers and payers often refer to these guidelines, especially for new technologies.

Aside from their role in helping providers to implement these technologies, guidelines can serve as an authoritative standard in the context of professional liability, along with the literature,

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382 CLIA program. Baltimore, MD: Centers for Medicare & Medicaid Services, 2005. Accessed May 1, 2006. http://www.cms.hhs.gov/clia/.

383 Borchardt PE. Pharmacogenomics: an in-house advantage? Drug Discovery Today 2006;11(12):1-3.

384 Ibid.

385 CLIA – Clinical Laboratory Improvement Amendments. Rockville, MD: US Food and Drug Administration, 2005. Accessed May 3, 2006. http://www.fda.gov/cdrh/clia/index.html.

386 Borchardt PE 2006.

conventional medical practice, and FDA-approved labeling.[387,388] Medical professional organizations (e.g., American Society of Clinical Oncology) and authoritative governmental bodies (e.g., the US Preventive Services Task Force) may have a role to play in developing practice guidelines for the use of PGx. Outside of the US, agencies such as the National Institute for Health and Clinical Excellence (NICE) in the UK provide guidance regarding proper use of prescription medications and when PGx diagnostic tests are necessary for prescribing.[389] Given the potential complexity of PGx products, guideline developers may play an especially important role in facilitating the adoption of PGx products. Evidence-based guidelines will help providers determine when to order PGx tests, which drugs should be prescribed and at what dose, and whether PGx use should be reimbursed.[390]

Given that PGx is a relatively new area of research, there is only nascent activity in evidence-based practice guideline development for PGx.[391] Although there are relatively few practice guidelines pertaining to PGx in comparison to other health care topics, as evidence becomes available, professional associations and other groups are seeking to translate this information into guidelines for health care professionals. Guidelines from groups such as the American Society of Clinical Oncology and the College of American Pathologists have been published in recent years pertaining to HER-2/neu testing and the use of tumor markers in gastrointestinal cancer.[392,393] The National Academy of Clinical Biochemistry (NACB) recently drafted guidelines and recommendations for the laboratory analysis and application of PGx in clinical practice. NACB recognizes the central role laboratories will play in PGx and the need for such guidelines, citing the rapid influx of knowledge about PGx, the lack of guidance on the use of this information, the transition happening in PGx from basic research to clinical application, and the unclear evidence that exists for such clinical application. NACB also determined that there may be some confusion about PGx among payers and regulators and cited the need for more education. Another guideline produced by a group of physicians addressed the use of PGx testing for CYP450 polymorphisms in psychiatry.[394] While development of these guidelines is an encouraging step, NACB also recognizes the need for more detailed guidelines in the future.[395]

A recent report of the Genetics and Public Policy Center addresses the importance of practice guidelines for the successful integration of genetic testing into practice.[396] Although related to

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387 Rothstein MA 2001.

388 Transcript of ninth SACGHS meeting – March 27, 2006.

389 Pharmacogenetics: ethical issues, 2003.

390 Phillips KA 2004.

391 Hampton T. Researchers draft guidelines for clinical use of pharmacogenomics. JAMA 2006;296(12):3-4.

392 Wolff AC, Hammond EH, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Journal of Clinical Oncology 2007;25(1):118-45.

393 Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. Journal of Clinical Oncology 2006;24(33):5313-27.

394 de Leon J, Armstrong SC, Cozza KL. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. Psychosomatics 2006;47:75-85.

395 Guidelines and recommendations for laboratory analysis and application of pharmacogenetics to clinical practice. Washington, DC: The National Academy of Clinical Biochemistry, 2006. Accessed October 12, 2006. http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/DraftGuidelines/Pharmacogenetics/.

396 Genetic testing practice guidelines: translating genetic discoveries into clinical care. Washington, DC: Genetics and Public Policy Center, 2006. Accessed March 8, 2007. http://www.dnapolicy.org/resources/Genetic_Testing_Practice_Guideslines.pdf.

genetic testing rather than PGx testing, many of the aspects described in this report pertain to the development of practice guidelines for PGx. These include the critical role played by health care provider organizations and other stakeholders in developing guidelines. In contrast to the prevailing "piecemeal approach" to guideline development, it proposes the need for a more centralized mechanism for guideline development, including a sustainable source of funding and support from the federal government.

Each of the four types of gatekeepers described here plays a complementary role in enabling the use of new medical technologies in clinical practice. There will be a continued need for guidance from FDA, CMS and other agencies regarding how PGx products will be regulated, used in practice and reimbursed, and how PGx data may be used in health care decision-making, employment, insurance and other sectors. The degree of openness and transparency of these agencies regarding PGx will influence the extent to which innovators and manufacturers are willing to invest in the development of new PGx products, how the public will view PGx diagnostics, and how these elements will ultimately affect patient access to PGx. The following section describes in more detail the factors and challenges associated with implementation of PGx in practice.

IV. Implementation of PGx to Improve Outcomes in Clinical and Public Health Practice

The implementation of PGx in clinical practice should enable the provision of more personalized and effective health care. However, realizing the potential benefits of PGx depends on many factors. The following sections highlight the importance of education and guidance for health care providers, decision-makers and patients; the role of information technology; the emerging economic implications of PGx technologies; ethical, legal and social issues specific to the clinical implementation of PGx; and the need for coordination of HHS activities related to PGx.

A. Education and Guidance

Educational initiatives contribute to the ability of patients to know when to seek treatment, providers to deliver effective health care, and other health stakeholders to build the infrastructure and set policies to support clinical practice. As PGx tests and associated drugs become more widely available, it will be necessary to educate health care providers, patients, payers, and policymakers to support informed decisions regarding PGx.[397,398]

1) Health Care Providers

Health care providers, including physicians, nurses, pharmacists and other professionals, will play important roles in implementing PGx in routine practice. Although a range of health care providers will likely be involved in the delivery of PGx, those with prescribing ability (e.g., physicians, nurse practitioners, physician assistants) may be in a particularly important position to introduce PGx into patient care. Education and training for these and other providers regarding PGx will help to ensure that PGx technologies are used appropriately and effectively. Health care providers need information on PGx in order to provide accurate information to patients, know when to use PGx to make care decisions, interpret results of PGx tests, and provide or refer patients to counseling, as appropriate.[399]

The uptake of PGx testing and therapies will depend on acceptance by physicians, who are faced with complex concerns regarding their benefits, risks and costs.[400] Providers are challenged with maintaining currency about what tests are available; their accuracy, predictive validity and cost; which patients are most appropriate for testing; and how test results should inform therapeutic decisions.

Clinicians also must provide informed consent for genetic testing and, in some cases, arrange counseling. PGx tests may reveal unrelated, secondary information, in addition to the test result originally sought. For example, drug-metabolizing enzymes identified by PGx

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397 Frueh FW, Gurwitz D. From pharmacogenetics to personalized medicine: a vital need for educating health professionals and the community. Pharmacogenomics 2004;5(5):571-9.

398 Pharmacogenetics: ethical issues. London, England: Nuffield Council on Bioethics, 2003. Accessed April 25, 2006. http://www.nuffieldbioethics.org/fileLibrary/pdf/pharmacogenetics_report.pdf.

399 Phillips KA, Van Bebber SL. A systematic review of cost-effectiveness analyses of pharmacogenomic interventions. Pharmacogenomics 2004;5(8)1139-49.

400 Suther S, Goodson P. Barriers to the provision of genetic services by primary care physicians: a systematic review of the literature. Genet Med 2003;5(2):70-6.

diagnostics also may process environmental toxins; consequently, test results might reveal susceptibility to certain cancers.[401] The psychological effects of such a revelation can be considerable. As such, providers offering diagnostic testing with the potential to reveal damaging secondary information are advised to ensure that the test is performed at a CLIA-approved laboratory to ensure test accuracy. They also are advised to counsel patients about the possible risks and benefits of PGx testing. Should whole genome sequencing become widely available in the future, even more genetic information could be available for analysis, which would further underscore the importance of analytic accuracy and patient counseling.

When physicians recommend PGx testing, they need to integrate PGx test results with external factors, including possible drug interactions, in addition to costs and patient preferences, to determine treatment.[402,403] The complex informational needs of clinicians pose two challenges. First, understanding of the various factors that may affect clinical outcomes currently is limited. Second, many physicians do not currently possess the training to interpret the available PGx information.[404,405] In addition, there is evidence to suggest that physicians may not receive useful PGx information from drug labels. A recent review found available PGx information on drug labels to be inadequate for treatment decisions. Also, dosing recommendations based on PGx diagnostics are not well established.[406] The ability to overcome these challenges will affect the practical utility of PGx.

Some observers have called for professional bodies to play an active role in encouraging and facilitating education and training in PGx.[407] The National Coalition for Health Professional education in Genetics (NCHPEG) promotes "health professional education and access to information about advances in human genetics to improve the health care of the nation." Under contract to the Health Resources and Services Administration, NGHRI and the NIH Office of Rare Diseases, NCHPEG is coordinating genetic education programs for health professionals. In 2005, NCHPEG worked with the American Academy of Family Physicians (AAFP) to develop a series of web-based continuing medical education programs on genetically influenced health conditions as part of AAFP's 2005 annual clinical focus on genomics. NCHPEG also has developed a set of core competencies to help guide the development of educational initiatives in genetics and genetically-based health care.[408,409]

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401 Pharmacogenetics: ethical issues. London, England: Nuffield Council on Bioethics, 2003. Accessed April 25, 2006. http://www.nuffieldbioethics.org/fileLibrary/pdf/pharmacogenetics_report.pdf.

402 Burke W, Atkins D, Gwinn M, et al. Genetic test evaluation: information needs of clinicians, policy makers, and the public. Am J Epidemiol 2002;156(4):311-8.

403 Melzer D 2003.

404 Personalised medicines: hopes and realities. London, England: The Royal Society, 2005. Accessed April 25, 2006. http://www.royalsoc.ac.uk/displaypagedoc.asp?id=15874.

405 Pharmacogenetics: ethical and regulatory issues in research and clinical practice. Report of the Consortium on Pharmacogenetics, findings and recommendations. Minneapolis, MN: University of Minnesota, Center for Bioethics, Consortium on Pharmacogenetics, 2002. Accessed April 25, 2006. http://www.bioethics.umn.edu/news/pharm_report.pdf.

406 Phillips KA, Van Bebber SL 2005.

407 Hopkins MM, Ibarreta D, Gaisser S, et al. Putting pharmacogenetics into practice. Nat Biotechnol 2006;24(4):403-10.

408 Welcome to NCHPEG.org. Lutherville, MD: National Coalition for Health Professional Education in Genetics, 2006. Accessed May 4, 2006. http://www.nchpeg.org/index.asp.

409 Annual clinical focus 2005 genomics. Leawood, KS: American Academy of Family Physicians, 2006. Accessed May 5, 2006. http://www.aafp.org/online/en/home/clinical/acf/genomics.html.

SACGHS has recommended that health providers receive broad training about integrating PGx into their practices. This could include the development of educational models of clinical applications to help health professionals understand the benefits, application and ELSI components of PGx.[410]

It is also necessary to incorporate PGx education into medical school curricula.[411] Although not specific to PGx, the Association of American Medical Colleges (AAMC) recognizes the emerging importance of clinical training in genetics. As part of its Medical School Objectives Project, AAMC outlines specific recommendations on the attitudes, knowledge and core skills that graduating medical students should achieve in genetics. AAMC also provides recommendations for future genetics-focused educational needs in residency and practice.[412] The Accreditation Council for Graduate Medical Education, which is responsible for the accrediting post-MD medical training programs, outlines common requirements for graduate programs in molecular genetics, including curriculum requirements and core competencies.[413]

Other health care professionals, such as pharmacists and laboratory personnel, will need greater understanding of PGx.[414,415] Although pharmacy students receive some instruction in PGx, it is unclear whether the amount of instruction is adequate.[416] The American Association of Colleges of Pharmacy (AACP) is providing evidence-based materials on PGx to pharmacy students and practicing pharmacists. As part of AACP's web-based Curricular Resource Center, AACP provides a specific point of access to materials related to genetics and to PGx in particular.[417] The American College of Clinical Pharmacy provides continuing education credit for pharmacists who complete a course on the applications of PGx to patient care.[418]

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410 Resolution of the Secretary's Advisory Committee on Genetics, Health, and Society on Genetics Education and Training of Health Professionals. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, 2004. Accessed August 15, 2006. http://www4.od.nih.gov/oba/sacghs/reports/EducationResolutionJune04.pdf.

411 Personalized medicine: the emerging pharmacogenomics revolution. New York, NY: PricewaterhouseCoopers, 2005. Accessed April 25, 2006. http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf.

412 Medical school objectives project. Washington, DC: Association of American of Medical Colleges, 2006. Accessed May 7, 2006. http://www.aamc.org/meded/msop/start.htm.

413 Molecular genetics program requirements. Chicago, IL: Accreditation Council for Graduate Medical Education, 2006. Accessed May 7, 2006. http://www.acgme.org/acWebsite/RRC_130/130_prIndex.asp.

414 Pharmacogenetics: ethical issues, 2003.

415 Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.

416 Brock TP, Faulkner CM, Williams DM, Smith SR. Continuing-education programs in pharmacogenomics for pharmacists. Am J Health-Sys Pharm 2002;59:722-5.

417 Pharmacogenomics. Curricular resource center. Alexandria, VA: American Association of Colleges of Pharmacy, 2006. Accessed May 7, 2006. http://www.aacp.org/site/page.asp?TRACKID=&VID=1&CID=1039&DID=6100.

418 Pharmacogenomics: applications to patient care. Kansas City, MO: American College of Pharmacy, 2004. Accessed May 7, 2006. http://www.accp.com/strphgen.php.

Recommendations 10A & 10B

Health providers will need guidance on how to use PGx information when making clinical decisions. The following steps will help ensure that PGx technologies are effectively integrated into clinical practice.

10A. HHS should assist state and other Federal agencies and private sector organizations in the development, cataloguing and dissemination of case studies and practice models relating to the use of PGx technologies.

10B. HHS should assist professional organizations in their efforts to help their membership achieve established competencies on the appropriate use of PGx technologies. HHS also should encourage and facilitate collaborations between the organizations and the Federal government around these activities.

a) Clinical Practice Guidelines

Clinical practice guidelines are an important means of educating physicians, pharmacists, prescribing nurses, and patients about when PGx testing could be beneficial and how the test results should be used to inform treatment decisions.[419] Guidelines should be based on the current, best available evidence and consensus (though not necessarily unanimity) in the opinions of experts in the field, in order to be accepted by those involved in care delivery.[420] Agreement on established guidelines will be a challenge for developers due to the complexity and nascency of the field; however, the development of guidelines is vital to the successful and effective integration and implementation of PGx technologies.

Few PGx guidelines are currently available for a number of reasons (see Clinical Practice Guideline Developers in the Gatekeepers section for examples of existing PGx guidelines), including the relatively few PGx tests that are currently available and the paucity of evidence to support recommendations for use or guidance on how to use the test results to informed treatment decisions. Until evidence to support the development of clinical practice guidelines becomes more abundant, they will not be a primary tool for educating providers about PGx. The lack of practice guidelines will continue to affect providers' willingness to offer PGx testing to their patients.

Recommendation 10C

As evidence of clinical validity and clinical utility for a PGx technology accrues, HHS should support the conduct of systematic reviews and technology assessments to summarize the evidence base. These systematic reviews and technology assessments should be disseminated to professional organizations to facilitate the development of clinical practice guidelines.

b) Product Labeling

As part of approving new health products, FDA determines proper labeling to guide their use in clinical practice. As described above, drug labels describe the approved indications for use

[419] Personalised medicines: hopes and realities. London, England: The Royal Society, 2005. Accessed April 25, 2006. http://www.royalsoc.ac.uk/displaypagedoc.asp?id=15874.

[420] Grol R, Jalhuijsen J, Thomas S, et al. Attributes of clinical guidelines that influence use of guidelines in general practice: observational study. BMJ 1998;317:858-61.

and may specify dosing, contraindications, or other important instructions. Inclusion of genotypic information in drug labels can enhance their informational value to providers.

Two recent FDA guidance documents provide information regarding labeling for PGx products. In the 2003 draft guidance on PGx data submissions, FDA describes two main approaches to integrating PGx data into drug labeling: 1) including it in the drug label in an informational manner, and 2) specifying that dose selection or drug safety or efficacy is contingent upon the performance of a PGx test. In the first instance, the labeling is less restrictive. Such labeling may be appropriate when the PGx test is not considered to be a valid biomarker or when an FDA-approved or widely used commercial PGx test is not available. In the second instance, the labeling is more restrictive, and would be based on clinical trials in which patients were tested for drug metabolism genotype and dosed according to their test results, patients were selected for trial entry based on genotype or gene expression profile, or patients were excluded from the trial based on genotype or gene expression profile (e.g., markers for adverse event).[421] The 2006 draft guidance on PGx and genetic tests specifies that proposed labeling should include directions for use, quality control, instructions for interpretation of results, precautions, information on stability (i.e., shelf life) and performance (e.g., sensitivity, specificity), and in the case of PGx tests, limitations in testing for drug-metabolizing enzyme alleles (e.g., CYP2D6).[422]

In addition to these guidances, FDA is planning to release a new guidance pertaining to genetic information in drug labeling. According to an FDA official in February 2007, the agency will introduce a new format for drug labels that will include a PGx section and relevant genetic information in a prominent box.[423] The details of this guidance are uncertain, but its release will likely represent an important development for labeling of PGx products.

Currently, there are more than 20 approved drugs for which reference is made to predictive PGx testing in the drug labeling or package insert; examples include Herceptin and Gleevec.[424] A study published in 2006 found that PGx-based prescribing information is available in the published research literature for more than 70% of the top 200 most prescribed drugs. However, after examining the package inserts of these drugs, researchers found that package inserts for only three of these drugs contained PGx-based prescribing information to help guide therapy.[425] Another study analyzed 3,382 drug package inserts to determine how many contained PGx information and, of those with PGx information, what type of information was included. Only 76 (2%) of the 3,382 package inserts in the study contained PGx information and, of these inserts, only 25 contained PGx information that was sufficient to inform treatment decisions.[426] The investigators concluded that PGx-related data are only available in package inserts for a small

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421 Draft guidance for industry: pharmacogenomic data submissions. Rockville, MD: US Food and Drug Administration, 2003. Accessed March 21, 2006. http://www.fda.gov/cder/guidance/5900dft.pdf.

422 Draft guidance for industry and FDA staff: pharmacogenetic tests and genetic tests for heritable markers. Rockville, MD: US Food and Drug Administration, 2006. Accessed April 25, 2006. http://www.fda.gov/cdrh/oivd/guidance/1549.pdf.

423 Ray T. New FDA guidance will make genetic data more prominent in drug labels. GenomeWeb Daily News February 28, 2007. Accessed March 1, 2007. http://www.genomeweb.com/issues/news/138673-1.html.

424 Personalised medicines: hopes and realities, 2005.

425 Zineh I, Pebanco GD, Aquilante CL, et al. Discordance between availability of pharmacogenetics studies and pharmacogenetics-based prescribing information for the top 200 drugs. Ann Pharmacother 2006;40(4):639-44.

426 Zineh I, Gerhard T, Aquilante CL, et al. Availability of pharmacogenomics-based prescribing information in drug package inserts for currently approved drugs. Pharmacogenomics J 2004;4(6):354-8.

number of approved drugs and that the information provided currently is insufficient to inform clinical practice.

As more data are obtained regarding PGx tests and their predictive power and reliability are established, particular PGx tests may be incorporated more often into drug labeling.[427] FDA will need to consider the available evidence for diagnostics and drugs and the risk-benefit profile of these drugs in determining how to present PGx information on labels. For example, a drug-response genotype could be listed as a contraindication, a warning, or a precaution to prescribing a drug. Depending on the drug and available evidence, a drug maker may seek labeling that expresses the need for a PGx test as a precaution rather than a more adamant contraindication. This inclination may depend on apparent tradeoffs of expanding the use of a drug and concerns about legal liability in the event patients experience ADRs.[428]

When considering labeling for PGx products, it is also important to note that there are practical and statutory challenges. For example, there is uncertainty regarding whether FDA has the statutory authority to mandate cross-labeling of PGx tests and drugs and concern that cross-labeling will slow the labeling process.[429] Cross-labeling is just one of the issues that may need to be addressed in order to ensure that labeling is a source of useful information as PGx products are integrated into clinical practice.

Physicians are not bound by labeling, and can prescribe an approved product for off-label indications based on their professional medical judgment. Off-label use can include use of a drug in populations with contraindicated PGx test results or that were not included in clinical trials. Where PGx product labeling specifies that a particular PGx test result should be obtained before a drug is indicated, use of a drug without completing a required PGx test can also constitute off-label use. Off-label use also may occur if dosing guidance based on PGx test results on the drug labels is not straightforward or specific and results in an incorrect dosing decision.

Some regulators are concerned that off-label use may hinder safe diffusion of PGx products.[430] Although third-party payers cover particular instances of off-label use, such as for certain oncology therapies, reimbursement for off-label use is uncertain and may result in non-coverage and non-payment from third-party payers.[431]

The medical, legal, and ethical consequences of off-label use of PGx may be more complex than in other cases of off-label drug use.[432] Physicians who prescribe a drug without performing the requisite PGx test may be assuming a greater burden for any ADRs or other adverse events that may be associated with off-label use. Alternately, a patient may ask for and receive a drug for

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427 Robertson JA 2002.

428 Robertson JA, Brody B, Buchanan A, Kahn J, McPherson E. Pharmacogenetic challenges for the health care system. Health Affairs 2002;21(4):155-67.

429 Evans BJ. What will it take to reap the clinical benefits of pharmacogenomics. Food and Drug Law Journal 2006;61(4):753-94.

430 Melzer D 2003.

431 Off-label use of anticancer therapies: physician prescribing trends and the impact of payer coverage policy. Washington, DC: Biotechnology Industry Organization, 2005. Accessed April 26, 2006. http://www.bio.org/speeches/pubs/CovanceReport.pdf.

432 Evans BJ. What will it take to reap the clinical benefits of pharmacogenomics. Food and Drug Law Journal 2006;61(4):753-94.

which a particular PGx test result is required in product labeling before it can be prescribed. If their PGx test results do not support using the drug and the patient subsequently suffers an ADR, it is uncertain whether the prescribing clinician would be held liable for the ADR.[433] Given that off-label use of PGx exists and may become prevalent, exploring its implications may be important for ensuring proper delivery in practice and patient safety.

Readily available labeling information can support provider prescribing decisions. In an effort to keep this information current and easily accessible, FDA and NIH have started the DailyMed project. DailyMed includes FDA-approved package inserts, medication content information, and is available in both a web-based and downloadable format. This open, paperless resource is available for physician and public use, providing greater support for PGx testing and therapeutic decisions.[434,435]

Recommendations 10D & 10E

10D. FDA and drug and diagnostics manufacturers should focus more attention on ensuring that all relevant PGx information is included in drug and PGx test labels. The information contained in these labels should clearly describe the test's analytical validity and clinical validity and provide adequate and clear information for clinicians to use when making treatment decisions based on PGx test results (e.g., about dosing or drug selection).

10E. NIH and FDA should continue expanding the Internet-based DailyMed project, which provides up-to-date, real-time prescription drug label/package insert information to people who have Internet access. To ensure that all sectors of the public have access to this information, FDA and NIH should develop other ways to disseminate this information.

2) Other Health Decision-makers

Efforts to educate other health decision-makers, including policymakers, government officials and others, are also important for realizing the potential of PGx.[436] Among the many challenges for FDA and other regulatory bodies is having adequate in-house expertise in PGx to enable informed application of existing regulatory procedures (rules, guidance, etc.), perceiving when new guidance or regulations should be developed, interacting with the pharmaceutical and biotechnology industries, and understanding and regulating the use of PGx in conjunction with clinical trials. Limited awareness and understanding of the health, economic, and social impacts of PGx could influence development and use of these technologies.

For payers, access to expertise in PGx will be necessary for understanding whether indications for using PGx fall under covered health care benefits (e.g., distinguishing between preventive uses of PGx that may not be covered and diagnostic and monitoring ones that are), making evidence-based coverage decisions for particular PGx technologies, and making medical necessity

433 Personalised medicines: hopes and realities. London, England: The Royal Society, 2005. Accessed April 25, 2006. http://www.royalsoc.ac.uk/displaypagedoc.asp?id=15874.

434 About DailyMed. Bethesda, MD: US National Library of Medicine, National Institutes of Health, 2006. Accessed August 16, 2006. http://dailymed.nlm.nih.gov/dailymed/about.cfm.

435 DailyMed initiative enhancing patient safety through accessible medical information. Bethesda, MD: US Food and Drug Administration, Center for Drug Evaluation and Research, 2003. Accessed August 16, 2006. http://www.fda.gov/cder/regulatory/ersr/2003_02_13_dailymed/index.htm.

436 Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews 2004;3:763-9.

determinations for individual patients. Payers that weigh clinical and economic tradeoffs must have the expertise, insight, and evidence to do so for PGx interventions. As is the case for other types of health care technology, payers influence one another, both within and beyond their respective markets and beneficiary populations. Raising the level of awareness of PGx among key decision-makers at CMS, large state Medicaid programs, VHA, and major national and regional private plans will result in broader awareness of PGx among other US payers.

The Personalized Medicine Coalition (PMC) is a non-profit umbrella organization that aims to educate "policymakers, government officials and private sector healthcare leaders about the public and personal health benefits of personalized medicine." PMC is comprised of pharmaceutical, biotechnology, diagnostic and information technology companies; health care providers and payers; patient advocacy groups; industry policy organizations; major academic institutions; and government agencies. PMC works to engage stakeholders in the public policy arena in discussions about personalized medicine. PMC is currently undertaking a comprehensive survey of the many initiatives on personalized medicine within the federal government and in the private sector and plans to advocate for increased coverage by payers, including CMS, and public incentives to encourage the co-development of PGx tests and drugs.[437,438]

3) Patients and the Public

As PGx products become available, patients will need to be educated about diagnostic and treatment options to help them make informed treatment decisions. Information on PGx from authoritative sources has been tailored to patients and can be found on the Internet. For example, NIH provides on-line materials that help educate patients about personalized medicine.[439] Still, much of this information will need to be communicated to patients by their personal health care providers. Similar to providing information and consultation to patients regarding genetic tests, clinicians will need to be equipped and ready to provide current information (e.g., on what PGx tests are available, what information tests will and will not disclose), consultation on treatment choices based on the results of PGx tests, and adequately address consent and confidentiality concerns.[440]

Patient perceptions will influence the extent and pace of uptake of PGx. Most patient preference research to date has generally shown that patient concerns about PGx testing are focused on cost, lack of effective treatment options for those testing positive, privacy and discrimination concerns, limited predictive value, and negative impact on quality of life.[441] There is little evidence on whether patients are likely to make higher out-of-pocket payments for genetic testing or individualized drug therapies. A 1999 poll found that 66% of respondents said they would pay extra for a "genetically customized drug that you knew would work for you."[442] More systematic

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437 Abrahams E, Ginsburg GS, Silver M. The Personalized Medicine Coalition: goals and strategies. Am J Pharmacogenomics 2005;5(6):345-55.

438 Personalized Medicine Coalition home page. Washington, DC: Personalized Medicine Coalition, 2005. Accessed May 7, 2006. http://www.personalizedmedicinecoalition.org/index.php.

439 Medicines for you: studying how your genes can make a difference. Bethesda, MD: National Institute of General Medical Sciences, 2005. Accessed May 7, 2006. http://publications.nigms.nih.gov/medsforyou/index.html.

440 Pharmacogenetics: ethical issues, 2003.

441 Lerman C, Hughes C, Trock BJ, et al. Genetic testing in families with hereditary nonpolyposis colon cancer. JAMA 1999;281(17):1618-22.

442 Gorman C. Drugs by design. Time Magazine. January 11, 1999:1-3.

research with involving patients involved in care choices will provide insights into patient preferences that are likely to affect demand, particularly in situations where the results of PGx testing reveal modest increases in risk for common diseases or ADRs.

Recommendations 11A & 11B

11A. HHS should use existing public consultation mechanisms to engage the public in a constructive dialogue regarding the potential benefits, risks and limitations of PGx technologies. This dialogue should include an assessment of their perceptions of and receptiveness to PGx and their willingness to participate in clinical research studies involving these technologies.

11B. To inform the public about the availability, benefits, risks and limitations of PGx technologies, HHS should ensure that credible educational resources are widely available through Federal websites and other appropriate media.

a) Marketing to Consumers

Some PGx tests will evolve into consumer-use products that can be acquired over-the-counter (OTC) at retail pharmacies and drug stores, or via mail. Shift in the acquisition channel from prescription to OTC purchase will be accompanied by shifts in marketing efforts from providers to consumers. This raises concerns about the ability of consumers to know when testing is indicated, how to acquire the appropriate test in a timely and secure manner, how to conduct the test, how to interpret the results, and what to do with the results.

When using OTC PGx products, consumers may be in a position to make health-related decisions without professional guidance. Many consumers may rely on packaging and other materials for education about their care choices, highlighting the importance of accurate, simply-stated marketing materials.[443] Some groups have expressed concerns that inaccurate or overstated marketing materials may increase testing demand unnecessarily and increase spending with little or no benefit.[444] Many have expressed concerns about the potential for misinterpretation of PGx test results and misinformed consumer health decision-making, which could result in patients discontinuing a drug or altering the dosage without consulting a physician. These concerns have fueled a debate over whether OTC use, and DTC marketing to encourage this use, is safe and ethical for PGx products.[445,446,447] A recent evidence report on the use of genomic tests for ovarian cancer found that studies of a DTC campaign for BRCA1/2 testing suggest an increase in utilization, but the effect on whether tests were used appropriately was unclear.[448] Certain PGx tests, including some that are easy to administer and provide clear and readily interpretable results, may be suitable for OTC use.[449]

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443 A roadmap for the integration of genetics and genomics into health and society. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, 2004. Accessed May 2, 2006. http://www4.od.nih.gov/oba/sacghs/reports/SACGHSPriorities.pdf.

444 Gollust SE, Hull SC, Wilfond BS. Limitations of direct-to-customer advertising for clinical genetic testing. JAMA 2002;288(14):1762-7.

445 Phillips KA, Flatt SJ, Morrison KR, Coates TJ. Potential use of home HIV testing. N Engl J Med 1995;332(19):1308-10.

446 Gollust SE 2002.

447 Zitner A. Firms sell gene tests directly to public. Los Angeles Times. August 11, 2002:A1.

448 Genomic test for ovarian cancer detection and management. Evidence Report/Technology Assessment #145. AHRQ Publication No. 07-E001. Rockville, MD: Agency for Healthcare Research and Quality, Duke University Evidence-based

Many websites already advertise and offer genetic testing to consumers for many applications, ranging from testing for specific drug-metabolizing enzymes to genetic testing for tailored nutritional advice.[450] Consumer demand for OTC PGx products is likely to grow as more of these products reach the market.[451] Consumers who are armed with information from OTC PGx tests and consumer-oriented information about prescription drugs may approach clinicians with requests for specific drugs.[452] Projecting from its considerable influence on demand for prescription drugs, an increase in DTC advertising for PGx testing is likely to substantially affect patient demand.[453,454,455]

Some evidence suggests that patient demand for PGx tests for making drug prescribing decisions may be greater than for genetic testing revealing disease risks. Results from the 2000 National Health Interview Survey showed that only 1% of respondents reported having had any genetic test for cancer risk.[456] In contrast, there has been strong patient demand and advocacy for access to Herceptin and for expedited FDA approval of the initial indication for metastatic disease and more recent indication for recurrent disease.[457,458]

Currently, DTC advertising for health care products is subject to regulation by FDA and FTC. However, DTC advertisements for PGx products are not regulated stringently by either of these federal agencies, and FDA does not appear to have sufficient resources to focus efforts in this area.[459,460,461] To ensure that DTC PGx products are used safely and appropriately, some have called on FDA to examine the regulatory issues associated with DTC marketing of PGx products and suggested that new types of regulation may be necessary. Such groups as the Consortium on Pharmacogenetics have stressed the importance of strict enforcement of consumer protection laws, requiring vendors to provide clear and accurate information about the predictive value of PGx tests and how they should be interpreted.[462] The regulatory strategy for DTC PGx products may evolve as the number of approved DTC PGx products increases and experience is gained with these products.

Practice Center, 2006. Accessed February 23, 2007. http://www.ahrq.gov/downloads/pub/evidence/pdf/genomicovc/genovc.pdf.

449 Pharmacogenetics: ethical issues, 2003.

450 Health and DNA. Seattle, WA: Genelex Corporation, 2001. Accessed April 21, 2006. http://www.healthanddna.com.

451 Gollust SE 2002.

452 Rosenthal MB, Berndt ER, Donohue JM, Frank RG, Epstein AM. Promotion of prescription drugs to consumers. N Engl J Med 2002;346(7):498-505.

453 Gollust SE 2002.

454 Pearson H. At-home DNA tests are here. The Wall Street Journal. June 25, 2002:D6.

455 Rosenthal MB 2002.

456 2000 National Health Interview Survey, sample adult person section—public use. Hyattsville, MD: National Center for Health Statistics, 2000. Accessed April 21, 2006. ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2000/samaDult.pdf.

457 Friend T. Dying patients plead for unproven cancer drugs. USA Today. May 16, 2001:D.09.

458 Kondro W, Sibbald B. Patient demand and politics push Herceptin forward. CMAJ 2005;(173):347-8.

459 A roadmap for the integration of genetics and genomics into health and society, 2004.

460 Gollust SE 2002.

461 Letter to Tommy Thompson – December 8, 2004. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, 2006. Accessed October 11, 2006. http://www4.od.nih.gov/oba/sacghs/reports/DTCletter.pdf

462 Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.

B. Information Technology and PGx

The widespread adoption of electronic health records (EHRs) is a key element in implementing PGx into national and international efforts to improve the quality and efficiency of health care. At the individual patient level, EHRs enable portability, accessibility and maintenance of personal health information that can support use of PGx technologies. EHRs can support patient stratification based on genotype and phenotype to facilitate clinical research and therapeutic efficiency and effectiveness. Given the necessary provisions for data security and confidentiality, gaining access to EHR data across populations enables broader studies of disease stage mapping, epidemiological studies, outcomes research and post-market surveillance.[463]

1) Electronic Health Records

After two decades of promise but slow diffusion, EHRs are beginning to demonstrate strides in improving health care delivery, particularly in certain large systems (e.g., VHA and DoD in the federal government, Kaiser Permanente plan in the private sector) and physician networks.[464,465] Aside from making the content of traditional medical records immediately available in multiple care sites, EHR systems offer higher-order capabilities such as clinical reminder systems, decision support tools, and data collection instruments. After implementing these systems, some providers have reported reductions in duplicate processes in health care delivery and improved clinical documentation, decision support, and workflow, allowing for more efficient patient care.[466] While EHR systems can improve care, they are expensive to install and require intense coordination between providers, developers and researchers to ensure interoperability.[467,468]

Regarding the potential benefits of EHRs, proponents note that these systems are not just "word-processed" medical records.[469] Multiple functions of EHRs offer means to enable development, validation, diffusion, payment, and evaluation. When configured as decision-support tools, EHRs provide systematic internal models that capture clinical information, aiding clinicians in diagnosing conditions and following care guidelines based on the patient input.[470] These tools allow physicians and other team members to rapidly transfer evidence-based knowledge and guidelines to coordinate patient care.[471] Reminder systems provide clinicians with evidence-based clinical reminders of care guidelines based on a patient's

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463 Think research: using electronic medical records to bridge patient care and research. Washington, DC: FasterCures, The Center for Accelerating Medical Solutions, 2005. Accessed March 7, 2006. http://www.fastercures.org/pdf/emr_whitepaper.pdf.

464 Kemper AR, Uren RL, Clark SJ. Adoption of electronic health records in primary care pediatric practices. Pediatrics 2006;118(1):e20-4.

465 Garrido T, Jamieson L, Zhou Y, et al. Effect of electronic health records in ambulatory care: retrospective, serial, cross sectional study. BMJ 2005;330(7491):581.

466 Guite J, Lang M, McCartan P, Miller J. Nursing admissions process redesigned to leverage EHR. J Healthc Inf Manag 2006;20(2):55-64.

467 Kemper AR 2006.

468 National Health Information Infrastructure. Washington, DC: US Department of Health and Human Services, 2006. Accessed August 4, 2006. http://aspe.hhs.gov/sp/NHII/FAQ.html.

469 Sujansky WV. The benefits and challenges of an electronic medical record: much more than a "word-processed" patient chart. West J Med 1998;169(3):176-83.

470 Ibid.

471 Dove JT. The electronic health record-the time is now. Am Heart Hosp J 2005;3(3):193-200.

condition.[472] Such EHR functions as decision-support and reminder systems may prove beneficial for PGx technologies, especially given the potential complexity of PGx test results and care that must be exercised when using results to make treatment determinations.[473,474]

PGx introduces particular considerations for EHR design, including which genetic records should be stored in EHRs, who should have access to the stored data, and how the data can be used to support decision-making for health providers. Storing an entire genome in an EHR may not yet be practical or useful, but storing the results of specific panels of genetic tests could be worthwhile for physicians to tailor individual patient treatment. These raw data could be accessed by a physician for review, and analyzed by a computer program as a decision-support tool that provides alerts and reminders.[475]

It is difficult to obtain accurate and current information on how many providers have adopted EHRs, because the system components vary so widely. As part of its Health IT Adoption Initiative, HHS has awarded a contract to The George Washington University and Massachusetts General Hospital/Harvard Institute for Health Policy, in partnership with the ONC, to measure the state of EHR adoption and determine the effectiveness of policies that are designed to speed up interoperability by increasing the adoption rate of EHRs.[476] The first of five annual reports were to focus on EHR adoption in multi-physician offices, single-physician practices, and hospitals, setting a baseline for measuring EHR adoption over time. As noted above, a significant hurdle to adoption of EHRs has been the lack of standards. HHS has awarded a contract to the Certification Commission for Health Information Technology (CCHIT) to create a standard for EHR certification, and vendors began to apply for certification in 2006.[477]

To help ensure the reliability and usability of EHR systems in clinical practice, several national initiatives, noted below, are currently focused on the development of and consistency between EHR systems. These have implications for the use of EHRs in PGx.

- **National Health Information Infrastructure (NHII)**. NHII is an HHS initiative focused on improving the effectiveness, efficiency, and quality of health care in the US. NHII is helping to promote interoperable systems that improve decision-making for those involved in health care delivery, including availability of a common set of standards for technology and nomenclature.[478,479]

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472 Sequist TD, Gandhi TK, Karson AS, et al. A randomized trial of electronic clinical reminders to improve quality of care for diabetes and coronary artery disease. J Am Med Inform Assoc 2005;12(4):431-7.

473 Goldstein MK, Coleman RW, Samson W, et al. Translating research into practice: organizational issues in implementing automated decision support for hypertension in three medical centers. J Am Med Inform Assoc 2004;11(5):368-76.

474 Schellhase KG, Koepsell TD, Norris TE. Providers' reactions to an automated health maintenance reminder system incorporated into the patient's electronic medical record. J Am Board Fam Pract 2003;16(4):312-7.

475 Mitchell JA. The impact of genomics on E-health. Stud Health Technol Inform 2004;106:63-74.

476 Office of the National Coordinator for Health Information Technology (ONCHIT): Health IT (HIT) Adoption Initiative. Washington, DC: US Department of Health and Human Services, 2005. Accessed April 25, 2006. http://www.hhs.gov/healthit/measuring.html.

477 Certification Commission for Health Information Technology home. Chicago, IL: Certification Commission for Health Information Technology, 2006. Accessed April 25, 2006. http://www.cchit.org/.

478 Federal efforts. Washington, DC: US Department of Health and Human Services, 2006. Accessed August 4, 2006. http://www.hhs.gov/healthinformationtechnology/federalEfforts.html.

- **Office of the National Coordinator for Health Information Technology (ONC).** Within HHS, ONC provides leadership for the development and implementation of a nationwide health information technology (HIT) infrastructure intended to enable secure and seamless exchange of data and records. ONC advises the Secretary of HHS on HIT policies and initiatives, and coordinates HHS efforts to meet the President's goal of making an electronic medical record available for most Americans by 2014. For PGx, improved interoperability of EHRs and other health systems may translate into greater ease for health care providers in accessing necessary information (e.g., test results) when making treatment decisions.

- **American Health Information Community (AHIC).** AHIC is a federal advisory body, chartered to make recommendations to the Secretary of HHS on how to accelerate the development and adoption of HIT. AHIC currently has three work groups working in areas of relevance to PGx and EHRs: The Personalized Health Care Workgroup is developing recommendations on standards for interoperable integration of genomic test information into EHRs and evaluating privacy and security issues associated with genetic tests;[480] the Confidentiality, Privacy and Security Workgroup is making recommendations to AHIC regarding the protection of personal health information;[481] and the EHR Workgroup is analyzing barriers to EHR adoption.[482]

- **Certification Commission for Health Information Technology (CCHIT).** CCHIT is an independent organization contracted by HHS to develop private sector certification criteria and a certification process for EHR products.[483] This certification is intended to ensure that electronic products meet certain functional levels, are interoperable with other systems, and comply with security criteria published by CCHIT.[484] With CHIT certification, EHRs used to capture PGx data will offer clinicians the advantages of interoperability while enhancing privacy protections for sensitive genetic information.

- **Human Genome Nomenclature Committee (HGNC).** Operating under the auspices of the Human Genome Organisation (HUGO), HGNC is a non-profit international effort to create standard symbols and names for genes. The pursuit of congruence in genomic semantics ultimately should help clinicians in entering consistent phrases and terms into EHRs for more efficient patient care. The goals of HGNC are especially applicable to the use of PGx in clinical practice, since the standard nomenclature should allow for clearer communication between clinicians and other health care professionals regarding a patient's particular

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[479] Letter to Secretary Michael O. Leavitt - February 8, 2006. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, 2007. Accessed August 15, 2006. http://www4.od.nih.gov/oba/sacghs/reports/HII_letter_to_Sec_02_08_2006.pdf.

[480] Personalized Health Care Goals. Washington, DC: US Department of Health and Human Services, 2006. Accessed March 19, 2007. http://www.hhs.gov/healthinformationtechnology/federalEfforts.html.

[481] Confidentiality, Privacy & Security Workgroup. Washington, DC: US Department of Health and Human Services, 2006. Accessed March 19, 2007. http://www.hhs.gov/healthit/ahic/confidentiality/.

[482] Electronic Health Records Workgroup. Washington, DC: US Department of Health and Human Services, 2006. Accessed March 19, 2007. http://www.hhs.gov/healthit/ahic/healthrecords/.

[483] CCHIT launches certification of ambulatory electronic health record products. Chicago, IL: Certification Commission for Health Information Technology, 2006. Accessed May 3, 2006. http://www.cchit.org/media/news.htm.

[484] News release: announcement to help speed adoption of electronic health records. Washington, DC: US Department of Health and Human Services, 2006. Accessed August 4, 2006. http://www.hhs.gov/news/press/2006pres/20060718.html.

genetic markers, consistent entry of this information into EHRs and other databases, and interoperability among EHR systems.[485,486]

These efforts, among others, should contribute to more effective integration of PGx into patient care. Still, there is no guarantee of widespread adoption of EHRs in the short term, because they face up-front implementation costs, may appear to be subject to obsolescence, and must demonstrate interoperability, utility, reliability, and affordability.

In addition to promoting the adoption of EHRs, there are efforts to increase the use of clinical decision support systems. Although widely recognized as important for facilitating the use of PGx and other technologies, implementation of these systems has been limited and, in many cases, these systems are still under development or have encountered roadblocks.[487] To reach the goal of widespread use of decision support in health care, the American Medical Informatics Association, with sponsorship from the ONC, has developed a strategic plan to advance clinical decision support.[488] Presented in June 2006 to HHS Secretary Mike Leavitt and AHIC, this plan considers barriers to widespread use of clinical decision support and proposes solutions for overcoming these challenges.[489]

2) Data Standards

Integration of PGx research and clinical data and the translation of this information into practice will rely on data standards. Harmonization of data standards for achieving interoperability of PGx databases and other health data and increasingly is becoming a high priority for the federal government. Efforts to adopt the use of EHRs and e-prescribing will require an infrastructure that allows for the accessibility and exchange of health data from one entity to another and will require data standards to make this exchange technically feasible.[490] This infrastructure will necessitate flexibility to accommodate future innovation and requirements such as those posed by PGx, including the ability to merge personal genomic data with clinical and laboratory data.[491]

The federal government is addressing the need for interoperable health IT and data standards through efforts such as the Consolidated Health Informatics initiative under ONC and through other federal efforts and initiatives.[492] For example, the American National Standards Institute

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485 Rosenbloom ST, Miller RA, Johnson KB, et al. Interface terminologies: facilitating direct entry of clinical data into electronic health record systems. J Am Med Inform Assoc 2006;13:277-88.

486 Shabo A 2006.

487 Osheroff JA, Teich JM, Middleton BF, et al. A roadmap for national action on clinical decision support. Bethesda, MD: American Medical Informatics Association, 2006. Accessed March 1, 2007. http://www.amia.org/inside/initiatives/cds/cdsroadmap.pdf.

488 Ibid.

489 Press release: AMIA releases the report A Roadmap for National Action on Clinical Decision Support, supported by the U.S. Department of Health & Human Services. Bethesda, MD: American Medical Informatics Association, 2006. Accessed March 1, 2007. http://www.amia.org/inside/releases/2006/cdsroadmap_061306.pdf.

490 HHS accelerates use of e-prescribing and electronic health records. HHS news release. Washington, DC: US Department of Health and Human Services, 2005. Accessed April 28, 2006. http://www.os.dhhs.gov/news/press/2005pres/20051005.html.

491 Shabo A 2006.

492 Office of the National Coordinator for Health Information Technology (ONCHIT). Consolidated Health Informatics. Washington, DC: US Department of Health and Human Services, 2006. Accessed April 28, 2006. http://www.hhs.gov/healthit/chiinitiative.html.

is under contract to HHS to convene the Health Information Technology Standards Panel, which will convene US Standards Development Organizations and other stakeholders to develop, test and evaluate a harmonization process for a set of health IT standards that support interoperability.[493] In September 2006, HHS announced a new personalized medicine initiative that includes the formation of a cross-agency group with representatives from NIH, FDA, CMS, and other agencies to focus on the integration of genomics into clinical information systems.[494]

In addition to data standards, the translation of PGx into practice will rely on the development and use of standards to evaluate evidence from PGx research, as well as strategies to improve the evidence base for PGx. Efforts also need to focus on sharing and dissemination of PGx information, not only among researchers but with health care providers, policymakers and the public. For example, while health care providers are concerned with the clinical value of PGx tests, the body of research on the clinical validity and utility of PGx tests is still small.[495]

Various clinical vocabulary and messaging standards for health data already exist. However, integration of these data standards will be a challenge. With regard to PGx, these standards also will need to support the exchange and use of patient-specific genetic information while maintaining a secure environment.[496] For instance, a standardized method of classifying and describing a drug response phenotype would allow for improved data collection and exchange from different clinical trials.[497]

In an ongoing effort to address the need for a national health IT infrastructure, HHS has identified uniform standards that are to be adopted across federal agencies. Among these are standards from the Systematic Nomenclature of Medicine (SNOMED), the Logical Observation Identifiers Names and Codes (LOINC), and Health Level 7 (HL7).[498] The Basal Adverse Event Report (BAER) is a standard data collection format for adverse events.

- SNOMED, a standardized medical vocabulary developed by the College of American Pathologists, was licensed by HHS in 2003. SNOMED Clinical Terms form the core of SNOMED, providing more than 357,000 hierarchical health care concepts with unique and logic-based definitions.[499,500] SNOMED will serve as the standard computerized medical vocabulary system for electronically coding terms in the "Highlights" section of prescription drug labeling.

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493 HHS awards contracts to advance nationwide interoperable health information technology. HHS news release. Washington, DC: US Department of Health and Human Services, 2005. Accessed April 24, 2006. http://www.hhs.gov/news/press/2005pres/20051006a.html.

494 Ferris N. HHS team tackles genetics, EHR integration. Falls Church, VA: Government Health IT, 2006. Accessed October 13, 2006. http://www.govhealthit.com/article96044-09-13-06-Web.

495 Need AC, Motulsky AG, Goldstein DB. Priorities and standards in pharmacogenetic research. Nat Genet 2005;37(7):671-81.

496 Shabo A 2006.

497 Gurwitz D, Lunshof JE, Altman RB. A call for the creation of personalized medicine databases. Nat Rev Drug Discov 2006;5:23-6.

498 Standards. Washington, DC: Office of the National Coordinator for Health Information Technology, 2005. Accessed April 28, 2006. http://www.hhs.gov/healthit/standards.html.

499 Standards, 2006.

500 Shabo A 2006.

- The laboratory portion of LOINC provides a system for facilitating exchange and pooling of laboratory results (e.g., cell counts from a complete blood count).[501] HHS adoption of LOINC will enable standardized electronic exchange of clinical laboratory test orders and results, as well as drug label section headers.[502]

- HL7 is a messaging standard system that allows for the communication and exchange of clinical information to help and improve the coordination of care (e.g., better coordination of admittance, discharge and transfer of patients). HL7 messages also can be used to convey LOINC codes to health care providers. HL7's Clinical Genomics Special Interest Group is focusing on the development of message standards to communicate genomic data. The group's mission is to bridge personal genomic data and clinical data to facilitate personalized medicine.[503,504]

- BAER is a standard set of core medical information for reporting ADRs and other adverse events being developed to address the considerable differences among adverse event reporting requirements promulgated by various federal agencies. It consolidates and strengthens the vast set of data elements that would otherwise be necessary to fulfill multiple agency requirements. BAER is undergoing review and testing by the federal agencies, with Federal implementation targeted for 2008.

These clinical vocabulary and other data standards are integral to developing an infrastructure for the integration and interoperability of PGx databases and clinical data sources.

Recommendations 12A & 12B

12A. The Office of the National Coordinator for Health Information Technology, through the activities of the American Health Information Community and in consultation with DVA and DOD, should take steps to ensure the inclusion of clinically validated PGx test results into patient records, along with decision support systems and tools to enhance appropriate test use and interpretation. Decision support systems and tools should include information about the availability of PGx tests, patients' test results, and relevant information for making treatment and dosing decisions.

12B. Until electronic health record systems become a universal feature of the health care system, HHS should identify other ways to make best clinical practices for PGx more readily available to health providers as they are developed.

C. Economic Implications of PGx

The rapidly increasing cost of health care is a major concern in the US. Technological innovation is among the most important drivers of those costs.[505] While new technologies may improve the length and quality of life and be recognized as cost-effective, they almost

[501] Logical Observation Identifiers Names and Codes (LOINC). Indianapolis, IN: Regenstrief Institute, Inc., 2006. Accessed May 3, 2006. http://www.regenstrief.org/loinc.
[502] Standards, 2006.
[503] Standards, 2006.
[504] Shabo A 2006.
[505] Chernew ME, Jacobson PD, Hofer TP, Aaronson KD, Fendrick AM. Barriers to constraining health care cost growth. Health Affairs 2004;23(6):122-8.

invariably increase total costs. As health insurance premiums increase, many people have no or inadequate coverage. Fewer employers are providing health insurance, and among those that do, benefits are curtailed and costs are increasingly shifted to employees and their families. Federal and state governments are being challenged to continue to provide coverage to employees as well as Medicaid and Medicare beneficiaries. PGx technologies are among those that are expected to contribute to increased health care spending and difficult choices about resource allocation in US health care.[506]

The development, adoption, and use of PGx will be mediated by the effect of test use on health care costs. Diffusion of PGx technologies into clinical practice will entail cost changes (e.g., different unit costs of tests, test volume, pre-test and post-test genetic counseling, resulting changes in downstream use of health care services and type and number of health events). Further, PGx testing will affect costs associated with behavioral changes in patients with new knowledge of their genetic-based risks.[507] While intended to result in more targeted use of therapies and reduction of adverse events, PGx testing, as do other forms of testing, can lead to overuse of health care products and services.

Even without overuse, PGx technologies, like many new technologies, are likely to increase health care costs, particularly in the short-term.[508,509] One example is the drug Herceptin, which is targeted toward the 25 to 30% of metastatic breast cancer patients whose tumors over-express the HER2 protein. The cost of Herceptin, estimated at $40,000 to $60,000 per patient per year, is steep for health plans and may be impractical for patients with large cost-sharing burdens for drug acquisition.[510,511,512] If similarly costly therapies were available for many patients with common conditions, the health care costs could be significant.

Although laboratory testing using more expensive PGx technologies may eventually be offset by downstream savings in patient management and avoidance of adverse health events, these savings may not accrue to the payer for that care. While PGx has the potential to improve patient management, health outcomes, and quality of life, payers will scrutinize the cost-benefit tradeoffs of these technologies. Even if they have lower unit costs, new effective technologies almost invariably increase total costs; net cost savings from new technologies are rare.

Once PGx tests are validated, the public health potential benefit and overall cost of these tests can vary. For conditions that are prevalent and/or chronic, such as adult diabetes, high blood pressure, and asthma, the potential benefits of PGx tests are likely to be substantial. While PGx testing for biomarkers associated with these types of diseases may be relatively inexpensive per

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506 Teutsch SM, Berger ML. Misaligned incentives in America's health: who's minding the store? Ann Fam Med 2005;3:485-7.

507 National coverage determinations with data collection as a condition of coverage: coverage with evidence development. Baltimore, MD: Center for Medicare & Medicaid Services, 2006. Accessed July 27, 2006. https://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8

508 Pharmacogenetics: ethical issues. London, England: Nuffield Council on Bioethics, 2003. Accessed April 25, 2006. http://www.nuffieldbioethics.org/fileLibrary/pdf/pharmacogenetics_report.pdf.

509 Personalized medicine. The emerging pharmacogenomics revolution. New York, NY: PricewaterhouseCoopers, 2005. Accessed April 25, 2006. http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf.

510 Neyt M, Albrecht J, Cocquyt V. An economic evaluation of Herceptin(R) in adjuvant setting: the Breast Cancer International Research Group 006 trial. Ann Oncol 2006;17(3):381-90.

511 Waltz E. GlaxoSmithKline cancer drug threatens Herceptin market. Nat Biotechnol 2005;23(12):1453-4.

512 Berenson A. A cancer drug shows promise, at a price that many can't pay. NY Times (Print). 2006 Feb 15:A1, C2.

test, the large number of people that would need to be tested could result in high total costs. In contrast, for rarer conditions, fewer people would require the tests, though the costs associated with the tests likely would be higher.[513]

There is a need to carefully examine the consequences of new technology investments, including in PGx, from the perspectives of patients, providers, payers, employers and society more broadly. There is clearly economic value to many of the desirable consequences: better health outcomes, a creative research enterprise, a vibrant private sector, job creation, greater productivity, and stimulating innovation. On the other hand, there are ever-increasing costs that yield small returns on health in many instances and divert resources from other productive investments in health care and other sectors.

1) Cost-effectiveness

Successful translation of PGx tests and therapies into clinical practice and policy likely will depend on demonstrating their cost-effectiveness relative to standards of care, across the continuum of care.

For a PGx test, effectiveness can be assessed for:[514,515,516]

- Clinician ability to use or perform test
- Timeliness/turnaround of test results
- Test accuracy (sensitivity, specificity, predictive value)
- Clinician ability to interpret test results
- Impact on decision to prescribe therapy
- Impact on dosing of therapy
- Impact on surrogate outcomes (including biomarkers) or intermediate (short-term) outcomes
- Impact on long-term health outcomes and quality of life
- Impact on adverse events
- Impact on health care utilization

Cost-effectiveness analysis is used to quantify the marginal (difference in) cost per marginal unit of effectiveness achieved with a test versus the standard of care. Depending on its purpose, a cost-effectiveness analysis can be conducted from the perspective of the clinician, payer/health plan, patient, or society-at-large. Cost-effectiveness analyses are one type of economic analysis that can be used to evaluate health technologies or services. Pharmacoeconomics, which examines the costs and health outcomes associated with pharmaceutical treatments, may be particularly relevant to PGx.

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513 Personalised medicines: hopes and realities, 2005.
514 Veenstra DL 2000.
515 Wedlund PJ, de Leon J. Pharmacogenomic testing: the cost factor. Pharmacogenomics J 2001;1:171-4.
516 Goodman CS. HTA 101: introduction to health technology assessment. Falls Church, VA: The Lewin Group, 2004. Accessed February 27, 2007. http://www.nlm.nih.gov/nichsr/hta101/ta101_c1.html.

PGx tests will be used to narrow the target populations for certain therapies, including some new treatments that may provide health benefits to people with no or limited alternatives. As was the case with Herceptin, a new drug that offers even small improvements in health outcomes and is priced at tens or hundreds of thousands of dollars per patient per year, will raise difficult resource allocation decisions for payers. Coverage of costly interventions in one disease area limits resources for interventions in other disease areas. Therefore, major payers and other health authorities are increasingly interested in economic analyses that can inform these decisions.

Though more so in Europe, Canada and Australia than in the US, health authorities are using improvements in quality-adjusted life years (QALYs) and other outcome measures to compare cost-effectiveness of health care interventions.[517,518,519] Using cost per QALY as a unit enables comparisons of health care interventions across diseases and types of technologies, providing an indicator for the return on investment in health care. For example, in the UK, technologies with incremental cost-effectiveness ratios approaching £30,000/QALY tend to draw greater scrutiny by the National Health Service, although there is no formal cut-off level for inclusion as a health care benefit in that system.[520]

Cost per QALY is used informally as a means to gauge value-for-money by some commercial health plans, though not by Medicare.[521] While no formal threshold is used by US payers, there is informal recognition that incremental cost-effectiveness ratios of $50,000-$100,000 or more per QALY are high. It is also recognized that the ratios for many technologies in mainstream care exceed that magnitude.[522] Even though a PGx technology may confer a clinically significant improvement in health outcomes, doing so at a high cost may decrease payers' willingness to cover it or to pay a premium price for it, particularly in countries or among particular payers who formally consider cost effectiveness.

To date, very little research has been conducted on the cost effectiveness of PGx interventions.[523] Pharmacoeconomic analyses regarding PGx that have been conducted to date are regarded as exploratory and inconclusive; there is a need for further study in this area.[524, 525,526] One example of a recent economic analysis pertaining to PGx evaluated the use of genetic information to guide warfarin therapy.[527] This study concluded that the widespread use of genetic testing could result in an annual savings of $1.1 billion in health care costs, attributable to the

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517 Luce BR. What will it take to make cost-effectiveness analysis acceptable in the United States? Med Care 2005;43(7):II-44-8.

518 Siegel JE. Cost-effectiveness analysis in US healthcare decision-making. Where is it going? Med Care 2005;43(7):II-1-4.

519 Maynard A, Bloor K. Dilemmas in regulation of the market for pharmaceuticals. Health Aff 2003;22(3):31-41.

520 Guideline to the methods of technology appraisal. London, England: National Institute for Clinical Excellence, 2004. Accessed June 5, 2006. http://www.nice.org.uk/download.aspx?o=201973.

521 Neumann PJ, Rosen AB, Weinstein MC. Medicare and cost-effectiveness analysis. N Engl J Med 2005;353(14):1516-22.

522 Veenstra DL, Higashi MK. Assessing the cost-effectiveness of Pharmacogenomics. AAPS Pharmsci 2000;2(3):E29.

523 Phillips KA, Van Bebber SL. A systematic review of cost-effectiveness analyses of pharmacogenomic interventions. Pharmacogenomics 2004;5(8):1139-49.

524 Dervieux T, Bala MV. Overview of the pharmacoeconomics of pharmacogenetics. Pharmacogenomics 2006;7(8):1175-84.

525 Phillips KA 2006.

526 Phillips KA 2004.

527 McWilliam A, Lutter R, Nardinelli C. Health care savings from personalizing medicine using genetic testing: the case of warfarin. Washington, DC: AEI-Brookings Joint Center for Regulatory Affairs, 2006. Accessed February 28, 2007. http://www.aei-brookings.org/admin/authorpdfs/page.php?id=1337&PHPSESSID=5a612bb2e6f9e369bffbdc1f72d8e34c.

avoidance of serious bleeding events and strokes that may result when the dosing of warfarin is not properly managed.

As more economic research is conducted, PGx may be found to be more cost effective for certain uses or indications, such as when aiding rational drug selection for acute, life-threatening conditions where the cost of a time delay is high, or for chronic conditions where there currently is no well-validated way to assess outcome.[528,529] Regardless of the purpose of a PGx intervention, the makers of tests and therapies, including co-developed tests and drugs, are likely to seek the highest payment that the market can bear for realizing a tangible health benefit.

The extent to which manufacturers of technologies such as PGx are able to achieve a return on investment may influence their willingness to invest in PGx development. Therefore, as payers shift toward more explicit consideration of economic outcomes, members of industry also may focus greater attention on the potential economic outlook for their product development portfolios as they consider where to invest their R&D resources.

As PGx diagnostics become more readily available, it will be increasingly important to examine society's willingness and ability to pay for PGx tests without limiting access to underserved populations who cannot afford them.[530]

Recommendation 13

To ensure that investments in PGx are well-spent, HHS should gather data to assess the economic value of investments in PGx relative to other health-related investments. This assessment should encompass the cost-effectiveness of PGx technologies and take into account both the short- and long-term impacts on specific sectors and society as a whole.

D. Ethical, Legal, and Social Issues in Clinical Implementation of PGx

PGx may be associated with important social, ethical and legal issues. The concerns include access to care, protections of private health-related information, and legal liability for a range of health stakeholders, as described below.

1) Disparities in Access to Care for Underserved Populations

Disparities in access may arise from economic and cultural factors. As discussed above, PGx products that yield significant reductions in ADRs or improvements in health outcomes for selected population subgroups are likely to be priced at a premium.[531,532,533] The high cost of such PGx technologies may be offset, at least from a societal perspective, by reductions in downstream health care costs, including those resulting from avoided ADRs and decreases in

[528] Veenstra DL, Higashi MK, Phillips KA. Assessing the cost-effectiveness of pharmacogenomics. AAPS PharmSci 2000;2(3):E29.

[529] Need AC, Motulsky AG, Goldstein DB. Priorities and standards in pharmacogenetic research. Nat Genet 2005 Jul;37(7):671-81.

[530] Teutsch SM 2005.

[531] Pharmacogenetics: ethical issues, 2003.

[532] Personalized medicine: the emerging pharmacogenomics revolution. New York, NY: PricewaterhouseCoopers, 2005. Accessed April 25, 2006. http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf.

[533] Rothstein MA, Epps PG. Ethical and legal implications of pharmacogenomics. Nat Rev Genet 2001;2(3):228-31.

health care utilization. Competition may provide additional downward cost pressure. However, at the patient level, the high cost of PGx products is likely to appear in the form of higher co-payments for the insured and even higher financial hurdles for the uninsured and underinsured. This could add to disparities in access to care among low-income and other underserved populations, such as some racial and ethnic minorities who are more likely to be uninsured or underinsured.[534,535]

Some evidence indicates that the adoption of and access to new technologies among minority populations lags behind that of the general population, even after adjustments for insurance status.[536,537] In addition, minority populations are reported to have lower levels of trust for health care institutions.[538] Historical discrimination may increase fears of genetic discrimination, posing further barriers to adoption of PGx. Though public engagement and education on genetic issues may ameliorate some fears, public health officials will continue to face the challenge of ensuring that underserved populations receive necessary and equitable care.[539]

2) Stigma and Discrimination

Personal knowledge and sharing of PGx information raises concerns about the possibility of stigma and discrimination due to real and perceived risks. Patients and families may be concerned that information regarding one's response to a drug or susceptibility to health risks could be misused by employers or insurers. Beyond the harm that could be caused by the misuse of genomic information, risks perceived by patients and providers may raise barriers to adoption. In particular, patients may be reluctant to undergo a PGx test if they believe its results will be disclosed to health insurance companies that could use this information to drop or curtail patients' health care coverage or to current or prospective employers that could use it to limit employment opportunities, compensation, benefits or other terms.[540]

In a recent study of insurance denial rates, researchers found that individuals with genetic conditions were twice as likely to report having been denied health insurance than individuals with other chronic conditions. The study also reported that nearly 60% of study participants believed that a health insurance company can obtain their personal medical information without their permission. Individuals with genetic conditions were also more likely to report that their insurance company had limited coverage specifically related to their condition.[541]

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534 Smedley BD, Stith AY, Nelson AR, eds. Unequal treatment: confronting racial and ethnic disparities in health care. Washington, DC: National Academy Press, 2002.

535 Genomics and population health 2005. Atlanta, GA: Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention, 2005. Accessed April 25, 2006. http://www.cdc.gov/genomics/activities/ogdp/2005.htm.

536 Ferris TG, Kuhlthau K, Ausiello J, et al. Technology diffusion and inhaled corticosteroids for asthma. Med Care 2006;44(1):81-6.

537 Ferris TG, Blumenthal D. Investment, innovation, and disparities: a complex relationship. Health Aff (Millwood) 2005;[Epub ahead of print].

538 Smedley BD 2002.

539 Genomics and population health 2005. Atlanta, GA: Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention, 2005. Accessed April 25, 2006. http://www.cdc.gov/genomics/activities/ogdp/2005.htm.

540 Pharmacogenetics: ethical issues, 2003.

541 Genetic conditions more likely to lead to denial of insurance. The JHU Gazette 2007;36(23). Baltimore, MD: Johns Hopkins University. Accessed March 5, 2007. http://www.jhu.edu/~gazette/2007/26feb07/26gene.html

Current federal protection against genetic-based stigma and discrimination rests with provisions held in the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the Social Security Act, the Americans with Disabilities Act, HHS privacy standards of identifiable health information, the Civil Rights Act, the right to privacy established by the Constitution, and related judicial decisions. In addition, most states restrict the use of genetic information in insurance and employment settings, but these laws vary significantly.[542]

The increasing salience of genetic technologies and limited legal precedent have prompted divergent views on the extent of current protections. SACGHS and others contend that current regulations on the use of personal health information, including HIPAA and the array of state policies, may not protect patients adequately against misuse of genomic data. They argue that additional regulation is necessary to prevent discrimination and stigma and to overcome public fears.[543,544]

Other observers assert that current regulations protect patients adequately against stigma or discrimination on the basis of confidential genetic information. They argue that a perceived need for additional protection for genetic information is based on a fallacy of "genetic exceptionalism," which holds that genetic innovations pose entirely new challenges to the health care system and require entirely new solutions.[545] In addition, they suggest that, since insurance companies routinely refuse or modify coverage based on non-genetic factors that cannot be controlled by patients, regulations prohibiting health insurers from using such information in coverage decisions already establish special protections for genetic information, which is also not under the control of patients. It has also been suggested that establishing regulations that specifically protect against the misuse of genetic data may amplify public fears of misuse.[546,547]

Although there are numerous conceivable ways of misusing genetic information, the risks of such misuse are not well ascertained. Despite certain publicized flagrant abuses, the historical record of the abuse of health information is limited.[548] The sheer cost of collecting, sifting through, and interpreting genomic data may be enough to prevent health insurers from using the data in determining whether to offer insurance or to raise premiums.[549] However, widespread adoption of EHRs and continued efficiencies in computer science may lower such costs and enable analyses to support these decisions. Among the unknowns regarding the potential misuse of genetic information are that what appear to be unremarkable personal genetic data today may be revealed in future research as having considerable discriminatory consequence.[550]

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542 Ibid.

543 Ibid.

544 Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. JAMA 2001;285(5):540-4.

545 Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.

546 Burris S, Gostin LO, Tress D. Public health surveillance of genetic information: ethical and legal responses to social risk. In: Khoury M, Burke W, Thompson E (eds). Genetics and public health in the 21st century: using genetic information to improve health and prevent disease. Oxford, UK: Oxford University Press; 2000. Accessed April 25, 2006. http://www.cdc.gov/genomics/info/books/21stcentury.htm.

547 Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.

548 Kohane IS, Altman RB. Health-information altruists--a potentially critical resource. N Engl J Med 2005;353(19):2074-7.

549 Pharmacogenetics: ethical issues, 2003.

550 Kohane IS 2005.

Throughout its deliberations, SACGHS has emphasized the importance of federal non-discrimination legislation, and it gathered evidence in 2004 through requests for public comment and a hearing that documented fear of genetic discrimination in the US.[551] In an analysis of federal and state laws on genetic discrimination, SACGHS concluded that current laws do not comprehensively address concerns about use of genetic information, leaving substantial gaps in coverage and uncertain safeguards at best.[552] The Genetic Information Nondiscrimination Act of 2007, which was introduced in January 2007 in the House of Representatives and Senate, is intended to establish nationally consistent legal protections for patients. This bill is currently under consideration in committees of the House and Senate.[553,554,555]

3) Liability Considerations for Health Care Providers

The development and marketing of PGx tests and therapies raise new and complex legal issues for health care professionals who use these technologies. These legal matters will influence the uptake of PGx by health care providers and their patients.

Providers' exposure to liability depends on the accepted standard of care. Generally, standard of care for new health technologies is established in the medical literature, through use in practice, and via the development of clinical practice guidelines, and informed by FDA-approved labeling for regulated products. Providers could expose themselves to liability if an ADR occurs that could have been avoided had a PGx test been administered. Even in the few instances where a PGx test is clinically available, there is uncertainty about whether PGx testing is standard of care. In many cases, the literature on the clinical validity and clinical utility of the test is scant or non-existent, clinical practice guidelines are rare, and labeling content is limited or non-directive. On the other hand, PGx tests are being used in clinical practice and paid for by some insurers. This uncertain status of the standard of care for PGx testing raises questions about whether a physician would be liable for not ordering a test prior to prescribing a drug and at what point in the diffusion of the test would liability accrue.

Physicians and pharmacists also may be accountable for certain ADRs resulting from off-label use of PGx. Current regulatory policy may not address correct provider procedure in the instance that a patient wishes to be prescribed a drug that is indicated only in the presence of particular PGx test results, but refuses the associated diagnostic test. Such a situation could be interpreted as allowing the patient the right to a treatment even after having refused the test.

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551 Notice of meeting: Secretary's Advisory Committee on Genetics, Health, and Society. Federal Register 2001;69(168):53071.

552 Lanman RB. An analysis of the adequacy of current law in protecting against genetic discrimination in health insurance and employment. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, 2005. Accessed May 4, 2006. http://www4.od.nih.gov/oba/sacghs/reports/legal_analysis_May2005.pdf.

553 HR 493. Genetic Information Nondiscrimination Act of 2007. Washington, DC: 110th Congress of the United States of America, House of Representatives, 2007. Accessed February 28, 2007. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h493ih.txt.pdf.

554 Current status of GINA. Washington, DC: Coalition for Genetic Fairness, 2007. Accessed February 28, 2007. http://www.geneticfairness.org/act.html.

555 Given SACGHS's active interest in preventing genetic discrimination, the Committee has been in correspondence with the Department of Health and Human Services to support passage of genetic nondiscrimination legislation since the introduction of the Genetic Information Nondiscrimination Act of 2003.

This raises the question of who is responsible for an ADR if a physician prescribes the drug to a patient who refuses the associated diagnostic.[556]

Clinical application of PGx technology will require substantial education and training for such providers as primary care physicians, pharmacists, geneticists, and genetic counselors. This may further expose these providers to liability action, including subject to the "learned intermediary" and informed consent doctrines of tort law. Learned intermediary doctrine exacts a duty on drug manufacturers to warn prescribing physicians of a drug's potential adverse effects. Doing so may satisfy the manufacturer's duty to warn of a drug's dangers, even though the manufacturers may not have warned the end-user patients directly.[557] The doctrine of informed consent provides a basis for legal action where a physician fails to inform a patient of such adverse effects. Along with manufacturer warnings, the education and training of health care providers about PGx may increase their exposure to liability risks. Primary care physicians will be expected to know enough to refer patients who might benefit from gene-based drug therapy to genetic counselors and geneticists. Physicians who lack adequate knowledge and fail to properly refer patients whose health subsequently worsens could be subject to malpractice actions. If financial incentives or pressures from their managed health insurance plan are viewed as contributing to their failure to properly refer patients, they might be subject to actions pertaining to malpractice and breach of fiduciary duty.

Given that PGx-based diagnosis and therapy pose many challenges to ethical, legal, and social norms, it will be important for public and private entities to help resolve these issues. The collective participation of these entities, along with practical experience gained with the use of the first PGx-based products, can help to address these challenges.

Recommendation 14

NIH, in collaboration with other agencies, should continue to encourage and fund research on the ethical, legal and social implications of PGx. This research should include studies of whether integration of PGx into clinical and public health practice exacerbates health and health care disparities, limits access to or decreases the quality of health care, increases medical liability, or results in genetic discrimination.

E. Coordination of PGx Activities

The opportunities and challenges described in this report call for coordinated attention on the part of federal and state governments, drug and diagnostics manufacturers, researcher, health providers, payers, and organizations, among others. The complex nature of these challenges increases the difficulty of advancing practical and well-founded solutions. While many stakeholders work collaboratively on issues related to PGx and personalized medicine, a single, coordinated framework or action plan could prove beneficial to addressing these challenges.[558]

[556] Pharmacogenetics: ethical issues, 2003.

[557] Hall TS. Reimagining the learned intermediary rule for the new pharmaceutical marketplace. Seton Hall Law Rev 2004;35(1):193-261.

[558] Pharmacogenetics: ethical and regulatory issues in research and clinical practice, 2002.

Such a framework could help to better coordinate ongoing efforts such as those described in Appendix A and facilitate improved information sharing.[559]

Recommendations 15A & 15B

15A. An interdepartmental work group should be established to review SACGHS's PGx recommendations, assess whether and how to implement them, monitor HHS's progress, and report back to SACGHS. The work group also could serve as a forum for discussion of other PGx activities.

15B. HHS should assess the level and adequacy of resources being devoted to support the integration of PGx into clinical and public health practice to be sure gaps and opportunities identified in this report are addressed.

[559] Transcript of ninth meeting. Bethesda, MD: Secretary's Advisory Committee on Genetics, Health, and Society, March 27, 2006. Accessed May 4, 2006. http://www4.od.nih.gov/oba/SACGHS/meetings/March2006/transcripts/FullDayTranscript03-27.pdf.

V. Summary

A. The Promise of PGx

PGx has drawn great attention for its potential to alter the health care paradigm in the US and abroad. It provides a potentially powerful tool for personalizing medicine based on individual genetic variations. As such, it is anticipated that PGx may have an important role in addressing certain unmet health needs in the near and longer-term future. In the near term, for example, PGx offers a method for improving patient safety by identifying those patients at risk for ADRs. Given that many commonly prescribed drugs result in less than optimal therapeutic response, PGx offers a potential replacement for the traditional "trial and error" model of prescribing with more informed, patient-specific treatment selection.

Many of the unmet needs that PGx may address are longer term in nature. For instance, some have speculated that PGx may increase the cost-effectiveness of stratified drug development, thereby increasing the likelihood that drugs will be developed that are tailored to certain underrepresented demographic groups. PGx also offers a means for improving treatments for chronic diseases, thereby more dramatically reducing their overall burden. Finally, the use of PGx may help to improve the economic efficiency of the health system by curtailing the duration of illness through more effective treatments and minimizing the costs associated with ineffective treatment and avoidable ADRs.

Though few to date, the instances of translating PGx knowledge into practice have been noteworthy. For example, the pathway from concept to market for PGx products is being clarified by FDA, and diverse stakeholders in the field are building upon knowledge of ethical, legal and social issues. It will be important for these and other stakeholders to continually assess the influence of PGx on the health of our nation and the health system, to ensure that PGx is delivering on its promises to improve care and economic efficiency and help reduce disparities.

B. Challenges Facing PGx

Despite their promise, many challenges remain for PGx technologies, including considerable hurdles for demonstrating their value and enabling appropriate adoption in practice.[560,561,562] To date, few PGx products have reached the market and, of these, fewer have achieved third-party reimbursement. Among the constraints of development and diffusion of PGx into clinical practice is that current third-party payment mechanisms for diagnostic tests can discourage uptake of PGx tests and therapies by providers. The Medicare payment system for diagnostic tests is not well suited for recouping the research and development costs of these new tests. Also, the current health information infrastructure is not well-suited for PGx. Recent efforts by FDA and others to establish universal standards for PGx-related information systems will have to be expanded to enable system interoperability and flow of PGx information among providers.

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560 Tucker G. Pharmacogenetics – expectations and reality. BMJ 2004;329:4-6.

561 Hopkins, MM, Ibarreta D, Gaisser S, et al. Putting pharmacogenetics into practice. Nat Biotechnol 2006;24(4):403-10.

562 Schmedders M, van Aken J, Feuerstein G, et al. Individualized pharmacogenetic therapy: a critical analysis. Community Genet 2003;6)2):114-9.

Despite some progress in identifying ethical, legal and social challenges to PGx, actual and anticipated technical advances in the field are raising concerns about disparities in access to care among underserved populations and breaches in protection of confidential genomic information, among others.

C. Next Steps and Considerations for the Future of PGx

Realizing the promise of PGx as a tool to address unmet health needs and otherwise advance personalized health care depends on several key considerations, including those noted below.

- ***Clinical Research and Product Development*:** Adaptations to clinical trial and postmarket data collection may be necessary to assess accuracy and predictive value of PGx-based diagnostics as well as biological markers, intermediate endpoints, health outcomes and ADRs associated with PGx-based therapies in patient subgroups. This is likely to call for further regulatory guidance from FDA. Early communication with Medicare and other major payers may also inform premarket data collection. Given the scarcity of data on long-term health outcomes and potential cost savings associated with PGx, there is a need for more thorough, sustained post-marketing data collection to inform clinical practice, payment and related health policymaking.

- ***Regulation:*** There is a need for continued guidance from FDA regarding the agency's current thinking on data requirements and other aspects pertaining to market clearance and postmarket surveillance of PGx products. Diagnostic, pharmaceutical and biotechnology companies seek ongoing guidance from FDA for drug-diagnostic co-development and other regulatory matters pertaining to PGx. Of great relevance to development of PGx diagnostics and access to these will be any changes in the relative burdens of FDA and CLIA regulations pertaining to marketed tests versus laboratory-developed in-house tests. The degree of transparency and openness of communications with FDA regarding PGx will influence the extent to which industry is willing to invest in the development of new PGx products.

- ***Reimbursement***: Current coverage policies for PGx technologies underscore the importance of demonstrating clinical utility and value to payers. As more PGx products reach the market, payers will have more opportunities to develop and implement coverage policies, particularly in areas that are less familiar to payers, such as defining medical necessity in terms of genetic risk, multiplex tests, and drug-diagnostic combinations.

- ***Health Information Infrastructure***: As part of ongoing efforts to develop information technology systems in health care, systems are needed that accommodate the level of detail and type of data required for PGx-based treatment decisions, research and surveillance.

- ***Education***: Given such aspects as the role of genetics in PGx products, the particular attributes of linked PGx-based diagnostics and drugs, and specificity of PGx products to patient subgroups, there is a special need for education and training for physicians, pharmacists and other clinicians. The development, adoption, and use of PGx products will be influenced by provider competence with these technologies. Efforts to educate patients and the public about the use of PGx are equally critical for proper use of these technologies.

- ***Ethical, Legal and Social Issues***: The ethical, legal and social issues associated with PGx may influence the ability to develop PGx technologies, provider adoption, and patients' willingness to use them. Addressing these issues through well-crafted policy and guidance to providers is critical to ensuring the safe and successful application of PGx.

Ongoing discourse between public and private entities will be needed to address these and other as-yet unforeseen issues.

Appendix A:
Federal Efforts in Pharmacogenomics

In July 2005, the SACGHS Pharmacogenomics Task Force requested a review of federal activities related to pharmacogenomics to help inform its analysis of the gaps and overlap in federal efforts and to focus the development of recommendations. In response to this request, SACGHS staff used direct contact with agency representatives, websites, and relevant literature to compile the following summary of major activities. The activities listed below are based primarily on information obtained between July 2005 and January 2006.

Federal Efforts in Pharmacogenomics

Issues	Efforts Specific to PGx	General Efforts
	Research and Development	
Research ▪ *Federally-funded research efforts*	**NIH** 1. *Pharmacogenetics Research Network (PGRN) and PharmGKB* aim to advance knowledge of the genetic basis for variable drug responses, with the goal of translating this knowledge and identifying safe and effective drug therapies designed for individual patients. PGRN is comprised of twelve independently funded, multidisciplinary research groups, including the knowledge base group (PharmGKB), that conduct PGx research in an identified area. The work of these groups range from basic research into identifying variation in genes (and functional consequences) relevant to pharmacogenetics, to clinical research aimed at understanding the genetic basis for variable drug responses. http://www.nigms.nih.gov/Initiatives/PGRN 2. PROgram for GENetic Interaction (PROGENI) is the administrative and data coordinating center for the Interaction of Genes and Environment in Shaping Risk Factors for Heart, Lung, Blood, and Sleep Disorders Study. PROGENI coordinates the activities of a consortium of five separate NHLBI-funded studies - GET READI, GeneSTAR, GOLDN, GenSALT and HAPI – three of which (GOLDN, GeneSTAR, and HAPI) are performing PGx-related research. http://dsgweb.wustl.edu/progeni/ 3. Many NIH institutes support numerous investigator-initiated PGx research projects.	**NIH** The Molecular Libraries and Imaging initiative, part of the NIH Roadmap for Medical Research, includes a component on toxicology/predictive absorption, distribution, metabolism, and excretion (ADME). This component supports the development of datasets and analysis methods to allow better prediction of ADME and toxic properties of novel molecules. The goal is to help obviate the trial-and-error testing that accounts for a large proportion of the time, expense and failure in the use of small molecules as *in vivo* research tools and drugs. It includes elements that will facilitate the development of PGx tools. http://nihroadmap.nih.gov/molecularlibraries/

Issues	Efforts Specific to PGx	General Efforts
	FDA 1. Regulatory Scientific Research project on PGx Information in Drug Labels aims to assemble information of all drugs currently on the market with labels containing PGx warnings and/or information in a relational database. 2. CBER supports numerous investigator-initiated PGx research projects for product characterization. **Department of Veterans Affairs (VA)** VA supports a number of investigator-initiated PGx research projects.	
Novel Research Teams ▪ *Are new models for research needed to facilitate PGx?* ▪ *How will the research enterprise move away from discipline-specific and PI- driven research teams towards multidisciplinary research teams?*	**NIH** See PGRN on p. A-2	**NIH** The Research Teams of the Future theme of the NIH Roadmap seeks to encourage scientists to test a variety of models for conducting research. The three initiatives within this theme are: 1) High-Risk Research, 2) Interdisciplinary Research, and 3) Public-Private Partnerships. The initial awards funded planning grants for interdisciplinary research centers, innovative training programs, and the development of methodologies aimed at integrating behavioral and social science into interdisciplinary research. http://nihroadmap.nih.gov/researchteams/
New Drug Development ▪ *How will PGx be incorporated into drug development?*	**FDA** 1. *Guidance for Industry on Pharmacogenomic Data Submissions* provides drug developers with guidance on when PGx data submissions are required by the existing regulations and encourages voluntary genomic data submissions (VGDS). http://www.fda.gov/cber/gdlns/pharmdtasub.pdf	**NIH** NIH Summit Workshop on Predictive Drug Toxicology was held on June 15–17, 2004 to address the current understanding of drug-induced toxicities; discuss new procedures that may improve absorption, distribution, metabolism, excretion and toxicology (ADMET) analysis; and identify new techniques and research to prevent the selection of compounds that will fail in clinical testing. In this workshop, researchers from academia, the pharmaceutical

Issues	Efforts Specific to PGx	General Efforts
	2. VGDS facilitates the use of PGx and provide companies an opportunity to discuss their PGx data early in the approval process. The Genomics Group within the Office of Clinical Pharmacology of CDER and the Interdepartmental PGx Review Group has reviewed over 30 VGDS submissions. VGDS meetings associated with these submissions have led to open, thorough and productive scientific discussions about the preclinical and clinical application of PGx in drug development. http://www.fda.gov/cder/genomics/VGDS.htm 3. A series of joint FDA/EMEA PGx briefings, held under the FDA-EMEA Parallel Scientific Advice Program with industry sponsors, were conducted to develop consistent scientific and regulatory reviews and submission packages.	industry, and FDA described areas in which additional research is needed to improve predictive analyses and discussed what new science may be needed to improve preclinical testing to reduce the failure rate of drug candidates. http://nihroadmap.nih.gov/molecularlibraries/predictivetoxicology/index.asp
Diagnostics Development ▪ *How will development of PGx diagnostics be facilitated?*	**FDA** 1. *Draft Guidance on Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns* was issued in February 2003 for industry and FDA staff to facilitate discussions on how to prepare and review premarket approval submissions for multiplex tests or tests that assay multiple analytes simultaneously. 2. *Pharmacogenetic Tests and Genetics Tests for Heritable Markers* was issued in 2006 to further facilitate progress in the field of PGx and genetics. This draft guidance replaced the one above. http://www.fda.gov/cdrh/oivd/guidance/1549.html	**FDA** *Instrumentation for Clinical Multiplex Systems* and *Drug Metabolizing Enzyme Genotyping System* provide information on the classification of multiplex test systems and compliance requirements for special controls on Class II devices. http://www.fda.gov/cdrh/oivd/guidance/1551.html
Gathering Evidence on Post-market Drugs ▪ *How will the effect of PGx on adverse events be monitored?* ▪ *How will research on off-patent*	**NIH** 1. See PGRN on p. A-2 2. *Network of Pediatric Pharmacology Research Units* (PPRU) was established by NICHD in response to the need for appropriate drug therapy for pediatric patients. The PPRU Network facilitates and promotes pediatric labeling of new drugs or existing drugs. Through this process, the network strives to foster cooperative and complementary	**FDA** MedWatch, a component of FDA's Adverse Events Reporting Program, is the gateway for mandatory reporting of adverse events during premarket phases and the voluntary reporting during postmarket. http://www.fda.gov/medwatch/

Issues	Efforts Specific to PGx	General Efforts
drugs be done? Will retrospective studies be acceptable? Who will pay?	research efforts among academia, industry and health professionals. The overall goal of the network is the safe and effective use of drugs in children. Studies include phase 1 studies in developmental PGx. http://www.nichd.nih.gov/research/supported/ppru1.cfm 3. *Network to Study Drug-induced Liver Injury (DILIN)* is registry of patients who have experienced severe drug-induced liver injury. The registry will be used to conduct a prospective study of patients who recently suffered an adverse liver reaction after taking any drug or herbal medicine as well as a retrospective study of liver-induced injury from isoniazid, phenytoin, valproic acid, and clavulanic acid/amoxicillin. http://dilin.dcri.duke.edu/	
Evaluating Existing Tests ▪ *How will the value of PGx testing be evaluated?* ▪ *How can evidence on the use and outcomes associated with existing tests be accumulated?* ▪ *How will the barriers to implementation of PGx testing be identified?*	**CDC** *Evaluation of Genomic Applications in Practice and Prevention (EGAPP): Implementation and Evaluation of a Model Approach* is a model project that is implementing a coordinated process for evaluating genetic tests in transition from research to clinical practice in the US. The goal is to integrate knowledge from existing processes for evaluation and appraisal and the international health technology assessment experience in order to establish and evaluate a systematic mechanism for evaluation. The 13-member independent, multidisciplinary EGAPP Working Group identifies, prioritizes and selects topics and develops methods and approaches for evidence review and for generating recommendations based on the evidence. To date, four topics have been selected for review: two of these reviews have been completed, and one is currently being conducted by AHRQ's EPCs. A more targeted review of the fourth topic, *UGT1A1* testing in colorectal cancer patients treated with irinotecan, is being conducted through an internal process. Two of the four topics are new PGx tests; additional tests are under consideration. http://www.cdc.gov/genomics/gtesting/egapp.htm **AHRQ** Through an interagency agreement with CDC, AHRQ's EPCs have produced two evidence reports for EGAPP: *Genomic Tests for Ovarian Cancer Detection* and *Management* and	

Issues	Efforts Specific to PGx	General Efforts
	Testing for Cytochrome P450 Polymorphisms in Adults With Non-Psychotic Depression Treated With Selective Serotonin Reuptake Inhibitors (SSRIs). http://www.ahrq.gov/clinic/tp/genovctp.htm http://www.ahrq.gov/clinic/tp/cyp450tp.htm **NIH** NIGMS is developing an initiative to stimulate research on factors that determine implementation of basic PGx knowledge into clinical practice.	
Clinical Trials ▪ *How can PGx be incorporated into clinical trials?*	**VA** VA supports at least eight clinical studies with a PGx component. **NIH** PGx studies are included or planned in many of NIH's interventional clinical trials.	**NIH/FDA/VA** *Initiative on Methods, Measurement and Pain Assessment in Clinical Trials* (IMMPACT) includes among its secondary outcomes information about biological markers through PGx.

Issues	Efforts Specific to PGx	General Efforts
Outcomes Evidence ▪ *What is the optimal research design for determining effectiveness of PGx-based drugs?*		**AHRQ** The *Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network* is a network of research centers to conduct accelerated practical studies on the outcomes, comparative clinical effectiveness, safety and appropriateness of health care items and services. The network is comprised of research-based health organizations with access to electronic health information databases and the capacity to conduct rapid turnaround research. Initial research focuses on the outcomes of prescription drug use and other interventions for which randomized controlled trials would not be feasible or timely, or would raise ethical concerns that are difficult to address. In order to develop a method to obtain these data for comparative effectiveness research, AHRQ proposed a pilot methodological study to evaluate the feasibility of using a pharmacist-staffed call center to conduct outcomes evaluations of patients identified in a community pharmacy setting. This project will provide insight into whether pharmacists can be used to perform comparative effectiveness research.
		NIH *The Clinical Outcomes Assessment initiative*, a component of the NIH Roadmap, aims to support translational research by developing new technologies to improve the assessment of clinical outcomes. Technologies such as a computerized adaptive health assessment could revolutionize how symptoms and treatment outcomes are assessed. Equipped with these tools, scientists will be able to understand how patients perceive changes in their health status resulting from new treatments, thereby directing research to therapies that would be highly valued by patients. http://nihroadmap.nih.gov/clinicalresearch/overview-dynamicoutcomes.asp

Issues	Efforts Specific to PGx	General Efforts
Cost Analysis ▪ *What effect will PGx have on health care costs?* ▪ *Will PGx be cost-effective?*		**AHRQ** *The Research Initiative in Clinical Economics* defines and focuses AHRQ's agenda of research and activities relating to cost-effectiveness analysis (CEA), cost-benefit analysis, and related methods for estimating the value of health care interventions. AHRQ has initiated several projects to support the development of improved systems and mechanisms for using CEA to inform decision-making: 1) evaluation of economic analysis in formulary decision-making to facilitate and guide improvements in this process; 2) development of an innovative approach for allowing public citizens to provide informed input into resource allocation decisions; and 3) sponsorship of the July 2005 *Medical Care* supplement on decision processes using CEA and the potential and obstacles to wider use of CEA. Future projects building on these efforts will include development of a strategic plan for integrating cost-effectiveness considerations in health policy decisions. http://www.ahrq.gov/rice/
Oversight		
Safety & Efficacy ▪ *How are the safety and efficacy of PGx tests regulated?*	**FDA** FDA is charged with ensuring the safety and efficacy of drugs and medical devices marketed in the US. **FDA/CDC** FDA and CDC work with the Organization for Economic Cooperation and Development in identifying international initiatives and strategies relevant for PGx development and implementation to improve public health.	

Issues	Efforts Specific to PGx	General Efforts
Labeling ▪ *How will PGx data be incorporated into drug labels?* ▪ *What adverse events or efficacy thresholds will trigger labeling changes?*	**FDA** 1. CDER advisory committees have been asked to consider labeling changes for several drugs. For example, the Advisory Committee for Pharmaceutical Science held a meeting November 14-15, 2005 to provide guidance on PGx data integration into product labeling. The Committee recommended including information about genetic variants of CYP2C9 and KVORC1 in the warfarin label. 2. Regulatory Scientific Research project on Pharmacogenetic Information in Drug Labels (see p. A-3)	
Drug/Diagnostic Co-development ▪ *Models are needed to guide the process of drug-diagnostic co-development.*	**FDA** *Drug-Diagnostic Co-Development Concept Paper* was issued April 2005 to facilitate discussions on how to best prospectively co-develop drugs or biological therapeutics and device tests in a scientifically robust and efficient way. http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf	
Analytical Validity ▪ *How is the analytic validity of PGx testing assured?*	**CDC** 1. Two PGx tests (CYP450, UGT1A1) are being evaluated by the EGAPP Working Group (see p. A-5). 2. The *Genetic Testing Reference Materials Coordination Program* facilitates and coordinates information exchange between users and providers of quality control (QC) materials, and coordinates efforts for contribution, development, verification and distribution of QC materials for genetic testing. The program is currently working with the genetic testing community to define the QC material needs of PGx testing. Data on cell lines with known PGx genotypes has been collected and we are beginning to assess potential targets for QC material development. http://www.phppo.cdc.gov/dls/genetics/qcmaterials/	**CMS** All clinical laboratory testing performed on humans in the US are regulated by the Clinical Laboratory Improvement Amendments (CLIA) program.

Issues	Efforts Specific to PGx	General Efforts
	FDA/EPA/NIST *The MicroArray Quality Control (MAQC) project* aims to establish QC metrics and thresholds for objectively assessing the performance achievable by various microarray platforms and evaluating the advantages and disadvantages of various data analysis methods. The project will help improve microarray technology and foster its proper applications in discovery, development and review of FDA-regulated products. It involves six FDA centers, NIH, EPA, NIST, major providers of microarray platforms and RNA samples, academic laboratories, and other stakeholders. http://www.fda.gov/nctr/science/centers/toxicoinformatics/maqc/index.htm **FDA/NIST/NIH** *The External RNA Controls Consortium* (ERCC) involves three federal agencies in collaboration with academic and industry stakeholders in an effort to develop a set of 96 well-characterized external RNA spike-in controls for analysis of microarray and RT-PCR performance. ERCC has initiated the testing phase of the project, during which candidate external RNA controls will be evaluated in both microarray and QRT-PCR gene expression platforms. http://www.cstl.nist.gov/biotech/Cell&TissueMeasurements/GeneExpression/ERCC.htm	
	FDA/NIST FDA Office of Science funded a project for the development of standards for genomics technologies.	

Issues	Efforts Specific to PGx	General Efforts
Clinical Validity & Utility ▪ *How is the clinical validity and utility of PGx testing assured before and after tests are incorporated into practice?*	**CDC** Two PGx tests (CYP450, UGT1A1) are being evaluated by the EGAPP Working Group (see p. A-5). **NIH** See PGRN (p. A-2) **VA** 1. VA published a Request for Applications in 2006 to create a PGx analysis laboratory (PAL) to evaluate PGx data on the clinical utility of PGx tests. http://www.research.va.gov/funding/solicitations/docs/PAL_RFA.pdf	**NIH** NIH supports numerous investigator-initiated projects that aim to understand gene-disease associations, penetrance, expressivity, and genotype-phenotype correlations between genes and diseases, all of which provide crucial data for determining clinical validity of PGx tests.
Human Research Protections ▪ *In order to facilitate research and development efforts in PGx, should/can HRP regulations and policies be harmonized across the agencies?*		**OHRP** OHRP provides leadership and oversight on all matters related to the protection of human subjects participating in research conducted or supported by HHS. OHRP helps ensure that such research is carried out in accordance with the highest ethical standards and in an environment where all who are involved in the conduct or oversight of human subjects research understand their primary responsibility for protecting the rights, welfare and well-being of subjects. **FDA** In Title 21 CFR Part 50 is intended to protect the rights and safety of subjects involved in all clinical investigations regulated by FDA as well as clinical investigations that support applications for research or marketing permits for products regulated by FDA.

Issues	Efforts Specific to PGx	General Efforts
		NIH The Clinical Research Policy Analysis and Coordination (CRpac) initiative, a component of the NIH Roadmap, is addressing the difficulties clinical researchers confront in satisfying the multiple requirements of diverse regulatory and policy agencies. CRpac works with other agencies, institutional review boards, and other organizations to develop better processes and to standardize requirements for reporting adverse events, human subjects protections, privacy and conflict-of-interest policies, and standards for electronic data submission. http://crpac.od.nih.gov/ **VA** The Office of Research Oversight (ORO) serves as the primary VHA office in advising the Under Secretary for Health on all matters of compliance and assurance for human subjects protections. ORO promotes and enhances the responsible conduct of research in conformance with laws, regulations, and policies.
Direct-to-consumer Marketing ▪ *Is there any potential harm to individuals or the public as a result of DTC marketing of PGx tests and services?*		**FDA/FTC/CDC/NIH** A working group led by FDA is evaluating genetic tests advertised on the internet. **CDC/FDA/HRSA/NIH** A working group led by CDC is developing mechanisms to collect data on the public health impact of direct-to-consumer marketing of genetic tests. **CDC** CDC is collaborating with the Minnesota Department of Health to monitor use of direct-to-consumer genomic profiling available in the state.

Issues	Efforts Specific to PGx	General Efforts
	Education	
Public ▪ *Do patients have the information they need to make educated treatment decisions based on PGx testing?*	**NIH** NIGMS has developed two brochures, *Genes and Populations* and Medicines for YOU, to educate the public. http://publications.nigms.nih.gov/genepop/ http://publications.nigms.nih.gov/medsforyou/	**Surgeon General/AHRQ/CDC/HRSA/NIH** *The Family History Initiative*, a national public health campaign, encourages all families in the US to learn more about their family health history. The initiative also will help prepare the public for the future introduction of personalized medicine. http://www.hhs.gov/familyhistory/ **NIH** NHGRI developed media presentations related to public awareness and education about molecular biology and genetics issues. **HRSA** The Maternal and Child Health Bureau developed an educational tool to show the importance of family history and genetics.
Health Providers & Payers ▪ *Are providers prepared to use PGx information in clinical practice?* ▪ *Is there a need to convince physicians that PGx can be beneficial to patient health?* ▪ *Will sociological or cultural differences among health providers and medical specialties require tailored educational efforts?*	**HRSA/NIH** The National Coalition for Health Professional Education in Genetics (NCHPEG), which is funded by HRSA and NHGRI, is an "organization of organizations" that promotes health professional education and access to information about advances in human genetics and coordinates efforts for the education of health professionals. The theme of their 2007 annual meeting was PGx. http://www.nchpeg.org/	**HRSA** HRSA has dedicated significant resources towards genetics education of health care professionals, which include developing skills to work with diverse populations to enhance understanding of PGx information. The Bureau of Health Professions funded grants on education of health care professionals. Maternal and Child Health Bureau support educational projects to inform and educate various health provider groups. One of the education products developed by HRSA is the *Report of the Expert Panel on Genetics and Nursing: Implications for Education and Practice*, which provides recommendations on genetics education programming, interdisciplinary programs, collaboration and partnerships, and workforce issues. Another document, *Report of the Genetics Workforce Study*, provides recommendations for models for delivering clinical genetic services across several categories of services, settings, and geographic regions. **AHRQ** The Centers for Education and Research on Therapeutics (CERTs) demonstration program is a national initiative to conduct research and provide education that advances the optimal use of therapeutics (i.e., drugs, medical devices, and biological products).

Issues	Efforts Specific to PGx	General Efforts
	Clinical Practice	
Best Practices Guidance ▪ *Physicians need practical guidance on how to use PGx in clinical practice.*		**AHRQ** The Evidence-based Practice Centers (EPC) Program awards 5-year contracts to institutions in the US and Canada to review all relevant scientific literature and produce evidence reports and technology assessments on clinical, behavioral, organizational and financing topics. These reports are used to inform and develop coverage decisions, quality measures, educational materials and tools, guidelines, and research agendas. EPCs also conduct research on methodology of systematic reviews.
Integration ▪ *How can integration of PGx into clinical practice be facilitated?*		HRSA and NIH contracted with NCHPEG to coordinate efforts for the education of health professions in genetics between and among professional societies, for-profit corporations in biotechnology and pharmaceuticals, managed care organizations, consumer advocacy groups, academic institutions, and government agencies. This effort includes the development of a genetics search engine, GROW (Genetics Resources on the Web). The GROW search engine supports over 120,000 documents drawn from 24 participating sites, including those related to PGx.
Barriers to Uptake ▪ *What are the barriers to physician and patient use and/or acceptance of PGx? How can the barriers be addressed?* ▪ *Is the lack of adequate coverage and reimbursement a significant barrier?*	**HRSA** HRSA has a collaborative agreement with the Washington Department of Health to conduct a cost-effectiveness analysis on aminoglycoside-induced deafness.	**HRSA** The Maternal Child Health Bureau (MCHB) has two cooperative agreements with the Washington Department of Health on public policy and the economics of delivering genetic services including PGx. To date, surveys of the public identified a range of health, psychological, economic, social and global consequences of genetic testing. Surveys and interviews of health care providers and genetic testing laboratory directors revealed significant similarities and differences with public views. The project is expected to end in June 2007, at which time they will report research findings, and describe how these data can be used to inform educational programs and public policy.

Issues	Efforts Specific to PGx	General Efforts
	Infrastructure	
Electronic Medical Records ▪ *Are EMRs critical for the successful integration of PGx into clinical practice?* ▪ *Does PGx use increase in systems with functioning EMRs?*		**ONCHIT** The Office of the National Coordinator for Health Information Technology provides leadership for the development and nationwide implementation of an interoperable health information technology infrastructure to improve the quality and efficiency of health care and the ability of consumers to manage their care and safety. **VA** VISTA (Veterans' Health Information System and Technology Architecture) is an integrated clinical database and electronic medical records system that supports the daily management and delivery of health care services. CPRS is the medical record component, which includes laboratory test results, medical images, decision support, bar code medication administration, progress notes, and appointments. CPRS permits VA clinicians to access a patient's record from anywhere within the health enterprise at the point-of-care. **HRSA** MCHB has provided funding to the American Academy of Pediatrics (AAP) for the Partnership for Policy Implementation project. The project aims to develop AAP clinical guideline statements that can be "operationalized" to provide HIT standard-developing groups and software designers with specific, unambiguous content.

Issues	Efforts Specific to PGx	General Efforts
Developing Standards ▪ *Standards needed for reporting PGx in clinical practice in order to coordinate care* ▪ *Standards for research results in the literature and in the clinic in order to facilitate cross-study comparisons.*	**ONCHIT** *Consolidated Health Informatics Initiative* is a collaborative effort to adopt health information interoperability standards (health vocabulary and messaging). These standards will enable all agencies in the federal health enterprise to "speak the same language" based on common enterprise-wide business and information technology architectures. http://www.hhs.gov/healthit/chi.html **NIST** See MAQC project (p. A-10).	**ONCHIT** *HL7* has established a tentative standard that defines the set of functions needed in an electronic medical record. HHS continues to work with HL7 and others to define standards for transmitting complete electronic health records. http://www.hl7.org/ **NIH** NHGRI has funded the organization of academic conferences focused on information sharing and development of bioinformatics standards and potential collaborations. **HRSA** *The Health Disparities Collaboratives* include a patient registry to monitor disease management in patients served in Federally Qualified Health Centers. The patient registry includes a tool for the collection of a family health history. http://www.healthdisparities.net/hdc/html/home.aspx
Additional Resources	**VA** The Cooperative Studies Program is a large, multi-VHA center clinical trials program involving some 60 cooperative studies that including banking of DNA samples. The program aims to conduct clinical research on health issues that are vital to veterans; define research results that establish new standards of care and improve veterans' health; improve the efficiency of the VA health care system; and improve the health of the population as a whole. http://www1.va.gov/resdev/programs/blrd-csrd/csp.cfm	
Surveillance		
Public Health Impact ▪ *Will PGx improve public health?*		**HHS** See DTC data collection working group (p. A-12)

Issues	Efforts Specific to PGx	General Efforts
Adverse Events ▪ *How will adverse events associated with PGx testing be monitored?* ▪ *What threshold of severity and frequency of adverse reactions will trigger PGx testing?*		**FDA** FDA collects adverse events reports on drugs and devices that have been voluntarily submitted through its Adverse Events Reporting System.
Effectiveness ▪ *How can the effectiveness of PGx testing be monitored? (Also see outcomes research)*		**AHRQ** 1. The Integrated Delivery System Research Network (IDSRN) was developed to capitalize on the research capacity of, and research opportunities occurring within, integrated delivery systems. The network creates, supports, and disseminates scientific evidence about what works and what does not work in terms of data and measurement systems and organizational "best practices" related to care delivery and research diffusion. It also provides a cadre of delivery-affiliated researchers and sites to test ways to adapt and apply existing knowledge. http://www.ahrq.gov/research/idsrn.htm 2. The Healthcare Cost and Utilization Project (HCUP) is a family of health care databases and related software tools and products developed through a Federal-State-Industry partnership and sponsored by AHRQ. HCUP databases bring together the data collection efforts of State data organizations, hospital associations, private data organizations, and the Federal government to create a national information resource of patient-level health care data. These databases enable research on a broad range of health policy issues, including cost and quality of health services, medical practice patterns, access to health care programs, and outcomes of treatments at the national, State, and local market levels. http://www.ahrq.gov/data/hcup/
Unintended Consequences ▪ *Are there efforts to monitor any unintended clinical outcomes of PGx use?*		

Issues	Efforts Specific to PGx	General Efforts
Utilization Patterns ▪ *Who will be the main beneficiaries of PGx testing?* ▪ *Are there any efforts to monitor off-label uses of PGx?*		
	Coordination of Efforts	
Policy Directives ▪ *What is the level of attention and/or awareness of PGx within DHHS agencies?* ▪ *Where does PGx rank among DHHS and its agencies' priorities?*		**HHS** Secretary Leavitt's 500-day plan describes his vision of how the health care system will be transformed. Highlights include medications that are safer and more effective because they are chosen based on the patient's personal characteristics. http://www.hhs.gov/500DayPlan/500dayplan.html#HealthCare **FDA** The Critical Path Initiative which seeks to modernize drug development by making the process more predictable and successful, and less costly, identifies PGx as a key opportunity. http://www.fda.gov/oc/initiatives/criticalpath/
Networking/ Communication ▪ *The Committee identified a need to promote and facilitate data sharing. Are there established mechanisms for sharing PGx information?*	**NIH** PharmGKB is a publicly available Internet research tool developed by Stanford University with funding from NIH. The PharmGKB database is a central repository for genomic, phenotypic and clinical data information on participants of research studies at various PGRN medical centers. This database is available to the scientific community at large. (See PGRN and PharmGKB on p. A-2) http://www.pharmgkb.org/ **CDC** 1. The *Genomics & Public Health Conference* held in December 2005 considered ways to integrate genomics into large clinical trials and observational studies in order to increase evidence for medical decision making for applying genomic applications in clinical care and disease prevention. The group	**CDC** Human Genome Epidemiology Network (HuGENet™) is an information exchange network that promotes global collaboration in the development and dissemination of peer-reviewed epidemiologic information on human genes. It provides updated and accessible knowledge base on the World Wide Web for health providers, researchers, industry, government, and the public for making decisions involving the use of genetic tests and genomic interventions, including PGx, for disease prevention and health promotion. http://www.cdc.gov/genomics/hugenet/default.htm **AHRQ** *The Genomics & Medicine: How Do We Facilitate Clinical Translation of Gene-based Discoveries?* workshop held in October 2005 sought to identify knowledge gaps and other barriers to the clinical use of gene-based diagnostics and therapeutics; identify mechanisms to overcome these barriers, with a special focus on linking genetic/molecular information with

Issues	Efforts Specific to PGx	General Efforts
Networking/ Communication ▪ *The Committee identified a need to promote and facilitate data sharing. Are there established mechanisms for sharing PGx information?*	also considered ways to develop the infrastructure needed to conduct surveillance on the use of PGx and clinical genomics tests in the US. 2. A multidisciplinary workgroup comprised of clinicians, laboratory professionals, health care plan providers, information technology and resource experts, policy makers, educators, and others was formed to consider and implement initiatives needed to assure effective communication between clinical and laboratory settings when genetic tests are ordered and results reported.	longitudinal epidemiological/clinical outcomes data; and improve the coordination of ongoing federal and non-federal activities. **NIH/HRSA** The GeneTests Web site is a medical genetics information resource developed for clinicians and researchers to provide current, authoritative information on genetic testing and its use in diagnosis, management, and genetic counseling. GeneTests promotes the appropriate use of genetic services in patient care and personal decision-making. Support for GeneTests is provided through a contract with NHGRI, NCI and NLM and funding from HRSA. http://www.genetests.org/
Addressing Ethical, Legal and Social Issues		
Assuring Access ▪ *Will PGx increase the cost of drugs?* ▪ *Will companies pass along any savings from lower R&D costs to patients?* ▪ *If a validated PGx tests exists that identifies responders or those at risk for AEs, are physicians and insurers legally/ethically obligated to perform/pay for the test?* ▪ *Also, see Education issues*		

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Health and Health Care Disparities ▪ *Will PGx increase health and health care disparities?*		**Office of Minority Health** OMH improves and protects the health of racial and ethnic minority populations through the development of health policies and programs that will eliminate health disparities. OMH coordinated many of the HHS programs focused on reducing health disparities listed below. http://www.omhrc.gov/ *The Council on Health Disparities* was established to coordinate and unify HHS actions on disparities issues. The Council ensures that HHS contracts, conferences, grants and initiatives are aligned with the goal of enhancing and expanding the Department's role in reducing health disparities, including striving for racial and ethnic parity in the health professions. **HRSA** *The Health Disparities Collaboratives* is a system-wide quality improvement activity in Federally Qualified Health Centers that works toward eliminating health disparities. HRSA publishes the booklet *Eliminating Health Disparities in the United States* that outlines the agency's strategic direction for obtaining the overarching goal of 100% access to health care and zero health disparities. HRSA promotes outreach efforts to reach populations affected by health disparities to raise awareness about major health risks, including genetic risk factors and how to reduce these risks.

Issues	Efforts Specific to PGx	General Efforts
Allocation of Resources ▪ *Is there enough interest in PGx to draw the needed investment and resources to further its development?* ▪ *Does the promise of PGx warrant the resources needed for its full integration relevant to other health care needs?*		
Informed Consent ▪ *Does PGx present any unique issues that should be taken into account in the consent process?* ▪ *Will consent forms need to address group harms as well as potential physical harms to an individual?*		**NIH** See CRpac (p. A-12) **FDA** *Agency Emergency Processing Under Office of Management and Budget Review; Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens That Are Not Individually Identifiable* explains that it is possible in certain circumstances for *in vitro* diagnostic device studies to be conducted using leftover specimens obtained without informed consent while protecting the human subjects who are the source of such specimens. http://crpac.od.nih.gov/FinalFDAGuidanceonICforIVDDeviceStudieswithLeftoverSpecimensthatAreNotIndividuallyIdentifiable.pdf
Discrimination ▪ *How will the fear of discrimination affect the integration of PGx into health care?* ▪ *How can the fear of discrimination be addressed?*		**HHS** In a letter to SACGHS, the Secretary of HHS affirmed his commitment to work with Congress and relevant stakeholders to achieve passage of Federal genetic nondiscrimination legislation. http://www4.od.nih.gov/oba/sacghs/reports/letter_to_Sec_05_03_2005.pdf **VA** In October 2005, the Veterans' Disability Benefits Commission unanimously voted that a veteran's genetic makeup, which might show predisposition to certain illnesses before entering service, is not a reasonable topic for the Commission to study in its review of "service connection" and disability payments. http://www.vetscommission.org/october_14_2005/approved_minutes_10-14-2005[1].pdf

Issues	Efforts Specific to PGx	General Efforts
Privacy/Confidentiality ▪ *Are existing privacy protections adequate for the collection, use, and storage of genetic samples and information?*		**Office for Civil Rights** The privacy provisions of the Health Insurance Portability and Accountability Act of 1996 apply to health information created or maintained by health care providers who engage in certain electronic transactions, health plans, and health care clearinghouses. **NIH** See CRpac (p. A-12) **VA** The Veterans Health Administration (VHA) must comply with all applicable privacy and confidentiality statutes and regulations. There are six statutes and sets of regulations are especially relevant: PL 104-191, implemented by 45 CFR Parts 160 and 164, and U.S.C. 7332, implemented by 38 CFR §1.460-1.496, encompass or specifically include protection of genetic information.
Conflict of Interest		**VA** VA has developed policy to limit and manage conflicts of interest arising from business relationships between VHA staff and pharmaceutical industry representatives. VHA's National Ethics Committee has addressed the issue of *Gifts to Health Care Professionals from the Pharmaceutical Industry* http://vaww1.va.gov/vhaethics/download/Pharma_2003.doc Other agencies also have developed conflict-of-interest policies.
Intellectual Property ▪ *What will be the effect of patent restrictions on PGx R&D costs?* ▪ *What will be the effect of patent restrictions on access to PGx tests in clinical practice?*	**NIH** NHGRI issued an RFA on *Intellectual Property Rights in Genetics and Genomics* that aims to encourage study of the role of laws and policies regarding intellectual property rights in genetics and genomics research and development, and the effect of such laws and policies on progress in these fields and on commercialization, drug development, health care delivery, and the public health. http://www.genome.gov/10001618	**NAS** *Intellectual Property in Genomic and Protein Research and Innovation* is a project run jointly by the National Academies' Board on Science, Technology and Economic Policy and the Science, Technology and Law Panel and funded by NIH as well as a number of private organizations. The purpose of the project is to review patenting and licensing of human genetic material and proteins and their implications for biomedical research, therapeutic and diagnostic products and medical practice. The NAS report was released November 17, 2005. http://books.nap.edu/catalog.php?record_id=11487

Issues	Efforts Specific to PGx	General Efforts
Liability ▪ *Who is responsible for ensuring appropriate use of PGx testing?* ▪ *How will the legal system affect the adoption of PGx by clinical providers?*		**DOE** *Einstein Institute for Science, Health and the Courts* is a series of conferences for judges supported by a grant from the DOE Human Genome Program.
Social Consequences ▪ *Could certain PGx genotypes have associated stigma?* ▪ *What is the expected impact of PGx on use of race/ethnicity in tailoring drug treatment?* ▪ *Are there potential harms unique to PGx research or associated with participation in PGx research that should be considered?*	**NIH** NHGRI supports research relating to the ethical implications of PGx research involving racially identified populations; and establishment of a consortium of experts from law, genetics, public health and other disciplines to explore how information from the HapMap project will and should interact with preexisting social categories of race and ethnicity.	
Genetic Exceptionalism ▪ *Will PGx promote genetic exceptionalism or genetic determinism?* ▪ *Are there unique qualities of PGx relative to other genetic technologies?*		
Unintended Consequences ▪ *Are there any efforts to monitor or anticipate unintended ethical, legal, or social consequences?*		